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(54) Title: NOVEL INHIBITORS OF FARNESYL–PROTEIN TRANSFERASE

(57) Abstract

Novel compounds and pharmaceutical compositions are disclosed which are inhibitors of the enzyme, farnesyl–protein transferase. Also disclosed is a method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells. The method comprises administering the novel aminooxyamide compound to a biological system. In particular, the method inhibits the abnormal growth of cells in a mammal such as a human.

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NOVEL INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND

Patent application WO 95/00497 published 5 January 1995 under the Patent Cooperation Treaty (PCT) describes compounds which inhibit the enzyme, farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of Ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be additional compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

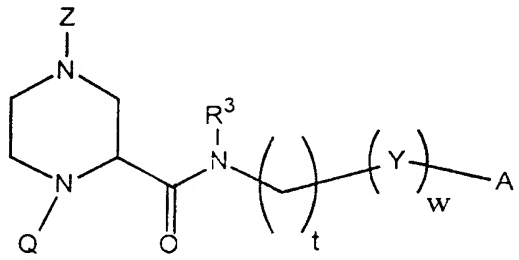
SUMMARY OF THE INVENTION

Inhibition of farnesyl protein transferase by compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic

change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

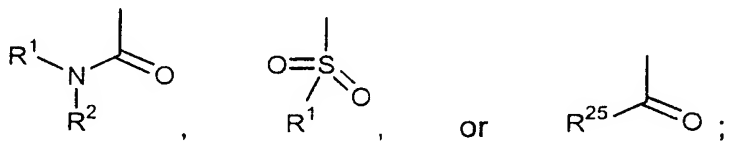
Compounds of the present invention are represented by Formula 1.0:



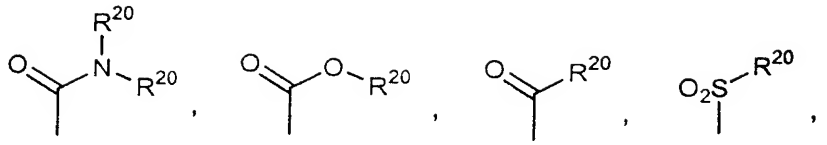
(1.0)

or a pharmaceutically acceptable salt or solvate thereof,

wherein Q is:



Z represents hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl,



heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, or -CY^3Y^4 wherein Y^3 and Y^4 independently represent alkyl and aryl or Y^3 and Y^4, together with the attached carbon atom (-C), can form a cycloalkyl or a cycloalkenyl ring;

wherein R^1, R^2, R^3, R^{20}, R^{22}, R^{30} and R^{32} independently represent hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R^{25} can represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl or -OR^{40} wherein R^{40} can represent alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

Y represents aryl, heteroaryl, heterocycloalkyl or cycloalkyl,

t is zero, 1, 2 or 3;

w is zero or 1; and

A is nothing, hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, cyano, heteroaryl or heteroarylalkyl.

In another embodiment, the present invention is directed toward a pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound (1.0) in combination with a pharmaceutically acceptable carrier.

In another embodiment, the present invention is directed toward a method for inhibiting the abnormal growth of cells, including transformed cells, comprising administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. Abnormal growth of

cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs, and (4) benign or malignant cells that are activated by mechanisms other than the Ras protein. Without wishing to be bound by theory, it is believed that these compounds may function either through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer, or through inhibition of ras farnesyl protein transferase, thus making them useful for their antiproliferative activity against ras transformed cells.

The cells to be inhibited can be tumor cells expressing an activated ras oncogene. For example, the types of cells that may be inhibited include pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells, prostate tumor cells, breast tumor cells or colon tumors cells. Also, the inhibition of the abnormal growth of cells by the treatment with compound (1.0) may be by inhibiting ras farnesyl protein transferase. The inhibition may be of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene. Alternatively, compounds (1.0) may inhibit tumor cells activated by a protein other than the Ras protein.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas,

such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma, melanoma, prostate carcinoma and breast carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an effective amount of the N-substituted urea compounds (1.0) described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the N-substituted urea compounds (1.0).

In another embodiment, the present invention is directed toward a method for inhibiting ras farnesyl protein transferase and the farnesylation of the oncogene protein Ras by administering an effective amount of compound (1.0) to mammals, especially humans. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

BOC - represents tert-butoxycarbonyl;

BOC-ON - represents [2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile];

C - represents carbon;

CBZ - represents benzyloxycarbonyl;

$ClCO_2Et$ - ethyl chloroformate;

CPh_3 - represents triphenylmethyl;

cycloalkyl-represents a saturated carbocyclic ring, branched or unbranched, of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

DBU - represents 1,8-diazabicyclo[5.4.0]undec-7-ene;

DCC - represents dicyclohexylcarbodiimide;

DCM - represents dichloromethane;

DIC - represents diisopropylcarbodiimide;

DIPEA - diiosopropyl ethylamine

DMAP - represents 4-dimethylaminopyridine;

DMF - represents N,N-dimethylformamide;

EDC (also DEC) - represents 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride;

EtOAc - ethyl acetate;

EtOH - ethanol;

Et_3N - triethylamine;

FMOC - represents 9-fluorenylmethyoxycarbonyl;

FMOC-Cl - represents 9-fluoroenylmethyl chloroformate;

HATU - represents [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate];

HOAc or AcOH - acetic acid;

HOBT - hydroxybenzotriazole;

Lutidine - 2,6-lutidine;

MCPBA - represents m-chloroperbenzoic acid;

Me - methyl;

MeOH - methanol;

$NaBH^5CN$ - sodium cyano borohydride

Ph - represents phenyl;

TBAF - represents tetrabutylammonium fluoride;

TFA - represents trifluoroacetic acid;

TFAA - trifluoroacetic anhydride;

THF - represents tetrahydrofuran;

M^+ -represents the molecular ion of the molecule in the mass spectrum;

MH^+ -represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

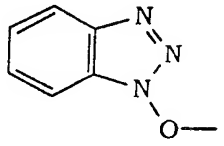
Bu-represents butyl;

Et-represents ethyl;

Me-represents methyl;

Ph-represents phenyl;

benzotriazol-1-yloxy represents



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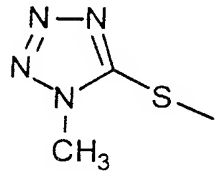
1-methyl-tetrazol-5-ylthio represents



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alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to ten carbon atoms, also preferably one to six carbon atoms; for example methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, n-pentyl, isopentyl, hexyl, isononyl and the like; wherein said alkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), aryloxy, $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} can independently represent hydrogen, alkyl, alkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms; wherein said alkenyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano (-CN), $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

alkoxy-an alkyl moiety of one to 20 carbon atoms covalently bonded to an adjacent structural element through an oxygen atom, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like; wherein said alkoxy group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), aryloxy, $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove;

aryl (including the aryl portion of arylalkyl) - represents a carbocyclic group of 6 to 15 carbon atoms containing one or two aromatic rings (e.g., aryl is phenyl); wherein optionally, said aryl group can be fused with one other aryl, cycloalkyl, heteroaryl or heterocycloalkyl ring provided that when the moiety "Z" in compound (1.0) is aryl, the fused aryl is a bicyclic ring (e.g napthalene) which is not a tricyclic or greater fused ring system; and wherein any of the available substitutable carbon and nitrogen atoms in said aromatic rings and/or said fused rings may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), aryloxy, $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$,

$-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove;

arylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more aryl groups, as defined above (e.g. arylalkyl is benzyl or phenylethyl); wherein optionally, said arylalkyl group can be fused with one other aryl, cycloalkyl, heteroaryl or heterocycloalkyl ring provided that when the moiety "Z" in compound (1.0) is arylalkyl, the fused arylalkyl is a bicyclic ring (e.g napthalenyl) which is not a tricyclic or greater fused ring system; wherein said arylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove;

cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms (e.g. cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like); wherein said cycloalkyl ring optionally can be fused with one other cycloalkyl, cycloalkenyl or heterocycloalkyl ring to form a bicyclic ring which is not a tricyclic or greater fused ring system; wherein any of the available substitutable carbon and nitrogen atoms in said cycloalkyl ring and/or said fused ring may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), aryloxy, $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove;

cycloalkylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more cycloalkyl rings as defined above; wherein

said cycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove;

cycloalkenyl - represents a carbocyclic ring having one or two unsaturated bonds (i.e. carbon to carbon double bonds) and containing from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms wherein said one or two unsaturated bonds do not impart aromatic character to the cycloalkenyl ring; wherein said cycloalkenyl ring optionally can be fused with one other cycloalkyl, cycloalkenyl or heterocycloalkyl ring to form a bicyclic ring (e.g. norbornenyl) which is not a tricyclic or greater fused ring system; wherein any of the available substitutable carbon and nitrogen atoms in said cycloalkenyl ring and/or said fused ring may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove;

cycloalkenylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more cycloalkenyl rings as defined above; wherein said cycloalkenylalkyl group optionally can be fused with one other cycloalkyl, cycloalkenyl or heterocycloalkyl ring to form a bicyclic ring (e.g. norbornylmethyl); wherein any of the available substitutable carbon and nitrogen atoms in said cycloalkenylalkyl group and/or said fused ring may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl. cyano (-CN), $-CF_3$, oxy (=O), $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$,

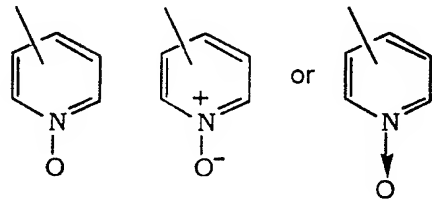
$-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove;

halo-represents fluoro, chloro, bromo and iodo;

heteroalkyl-represents straight and branched carbon chains containing from one to twenty carbon atoms, preferably one to six carbon atoms interrupted by 1 to 3 heteroatoms selected from -O-, -S- and -N-; wherein any of the available substitutable carbon and nitrogen atoms in said heteroalkyl chain may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove;

heteroaryl-represents cyclic groups having at least one heteroatom selected from O, S and N, said heteroatom(s) interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups containing from 2 to 14 carbon atoms (e.g. heteroaryl is imidazoyl); wherein said heteroaryl group optionally can be fused with one aryl, cycloalkyl, heteroaryl or heterocycloalkyl ring to form a bicyclic ring which is not a tricyclic or greater fused ring system; and wherein any of the available substitutable carbon or nitrogen atoms in said heteroaryl group and/or said fused ring may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, arylalkyl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove. Representative heteroaryl groups can include, for example,

furanyl, imidazoyl, pyrimidinyl, triazolyl, 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl N-oxide wherein pyridyl N-oxide can be represented as:

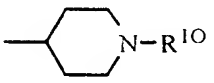


,

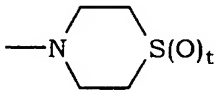
heteroarylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heteroaryl groups; wherein said heteroaryl group optionally can be fused with one aryl, cycloalkyl, heteroaryl or heterocycloalkyl ring to form a bicyclic ring which is not a tricyclic or greater fused ring system; and wherein any of the available substitutable carbon or nitrogen atoms in said heteroaryl group and/or said fused ring may be optionally and independently substituted with one, two, three or more of the following: wherein said heteroarylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-CH_2NR^{12}COR^{10}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove;

heterocycloalkyl-represents a saturated, branched or unbranched carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 heteroatoms selected from -O-, -S- and -N- , wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; wherein said heterocycloalkyl group optionally can be fused with one aryl, cycloalkyl, heteroaryl or heterocycloalkyl ring to form a bicyclic ring which is not a tricyclic or greater fused ring system; and wherein any of the available substitutable carbon or nitrogen atoms in said heterocycloalkyl group and/or said fused ring may be optionally and

independently and wherein any of the available substitutable carbon and nitrogen atoms in the ring may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), aryloxy, $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove. Representative heterocycloalkyl groups can include 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 1-, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 1-, 2- or 3-piperizinyl, 2- or 4-dioxanyl, morpholinyl,



or



wherein R^{10} is defined hereinbefore and t is 0, 1 or 2.

heterocycloalkalkyl- represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heterocycloalkyl groups; wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein said heterocycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, cycloalkyl, cyano (-CN), $-CF_3$, oxy (=O), aryloxy, $-OR^{10}$, $-OCF_3$, heterocycloalkyl, heteroaryl, $-NR^{10}R^{12}$, $-NHSO_2R^{10}$, $-SO_2NH_2$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}R^{12}$, $-NR^{12}COR^{10}$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{10}$ or $-COOR^{10}$, wherein R^{10} and R^{12} are as defined hereinabove.

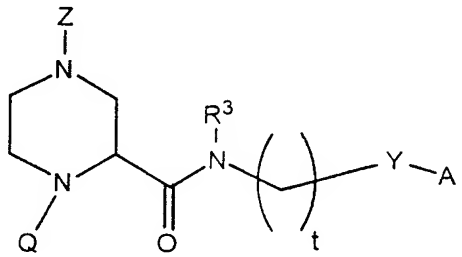
Certain compounds of the invention may exist in different stereoisomeric forms (e.g., enantiomers, diastereoisomers and atropisomers) . The invention contemplates all such stereoisomers both in pure form and in mixture, including racemic mixtures.

Certain compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may

include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purpopses of the invention.



(1.0)

Compounds of the present invention can be prepared according to the following Schemes.

Library Preparation. A library of compounds is prepared by parallel synthesis. A generic structure of these compounds is shown in Figure 1. The "A" group on the side chain histamine along with "Z" group on N-4 of the piperazine are varied in the library. Every member of the library contains methyl sulfonate at position N-1 of the piperazine core (Figure 1).

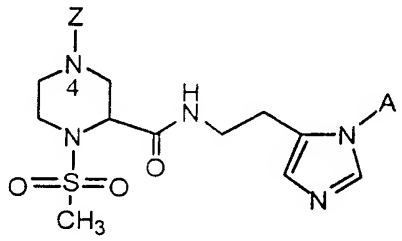
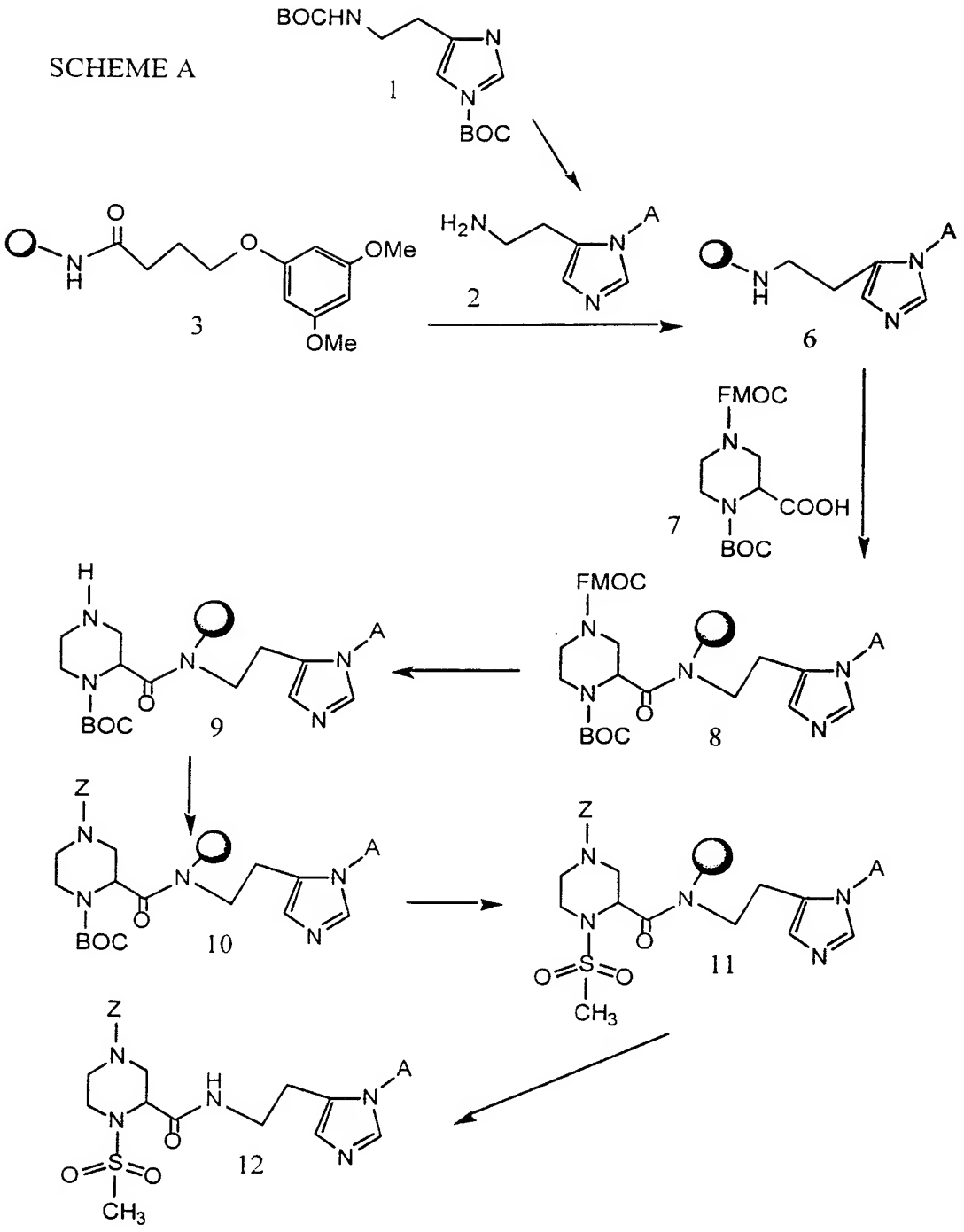


Figure 1

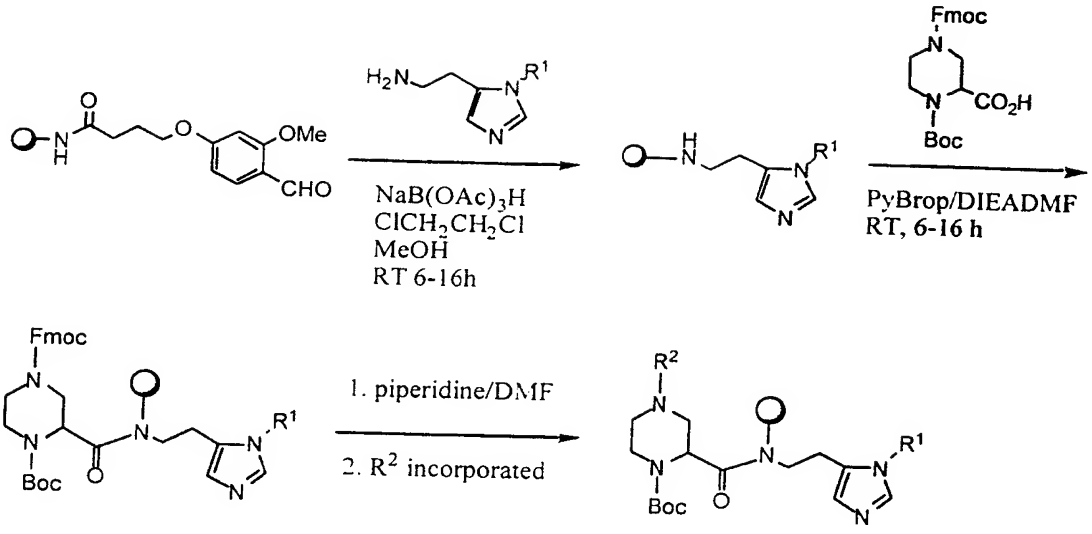
SCHEME A



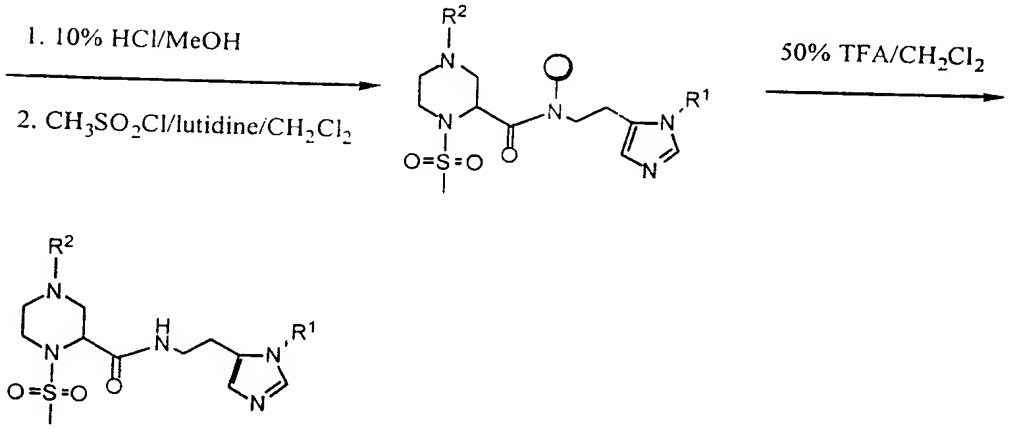
Referring to Scheme A, the side chain amines 2 were prepared by treating bis-Boc histamine 1 with the corresponding triflate, and subsequent removal of the Boc group. Library was prepared on TentaGel® (trademark of Rapp Inc., Germany) resin 3 functionalized with 4-(4-formyl-3-methoxyphenoxy)butyric acid 4 (shown in Scheme 1) to give functionalized

resin 5. TentaGel resin is a composite of low-cross-linked polystrrene and polyethylene glycol, which has been terminally amino functionalized. Synthesis was initiated in Merrifield shaker vessels with reductive amination of the side chain amines 2 using the aldehyde of the acid cleavable linker of the functionalized resin 5 to give 6. This was followed by coupling N-4-Fmoc N-1-Boc piperazine carboxylic acid 7 with 6 to give 8. Removal of the Fmoc group of 8 gives 9. Resin 9 was dried and loaded into Robbins FlexChem block (96 wells) and subsequent reactions were performed in the block. Resin 9 was reductively alkylated with a number of corresponding aldehydes with $NaBH_3CN$ in 2% HOAc in DMF or acylated with corresponding acid chlorides with lutidine in CH_2Cl_2 or sulfonyl chlorides with lutidine in CH_2Cl_2, or treated with isocyanates and DIPEA in CH_2Cl_2. Treatment of resin 10 with 10% HCl/MeOH followed by methanesulfonyl chloride gives resin 11. The product 12 is cleaved from resin 1 using trifluoroacetic acid.

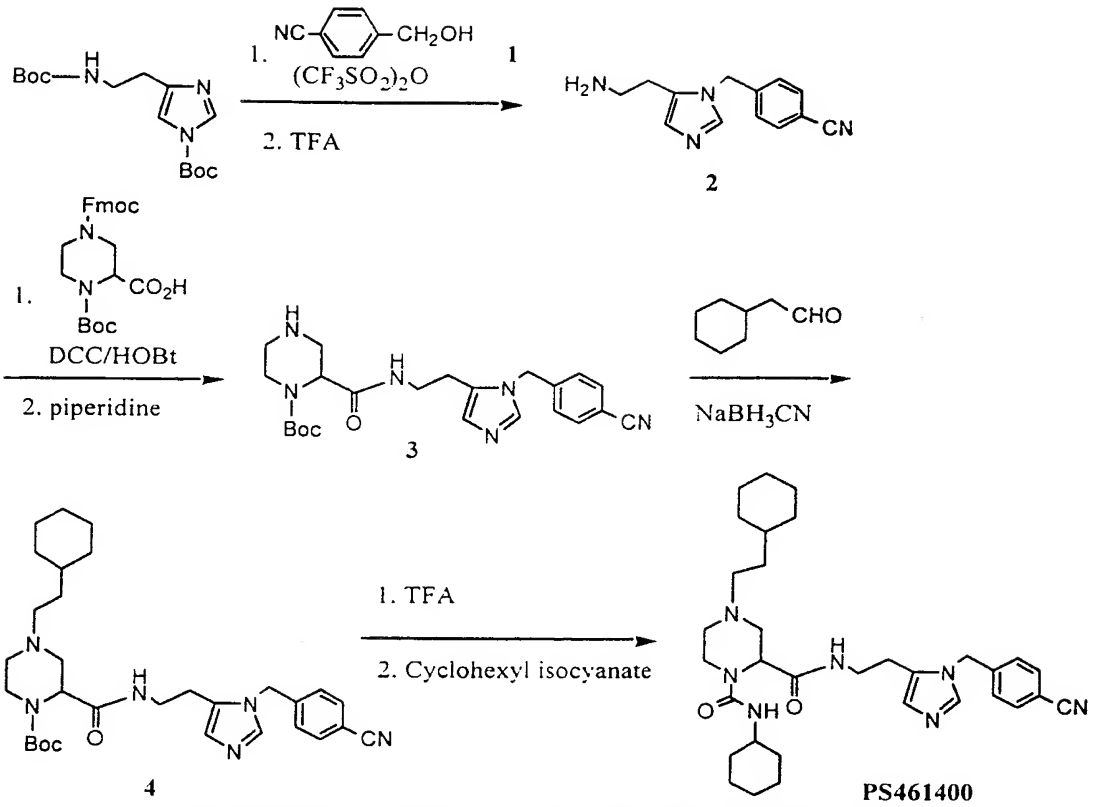
Scheme 1



when R^2	Reaction Conditions are:
$= COR_3$	R_3COCl, lutidine, CH_2Cl_2
$= SO_2R_3$	R_3SO_2Cl, lutidine, CH_2Cl_2
$= CH_2R_3$	R_3CHO, 2%HOAc/DMF, $NaBH_3CN$
$= CONHR_3$	R_3NCO, DIEA, CH_2Cl_2



Scheme 2



Preparation procedure for PS 461400 (Scheme 2)

1. Preparation of compound **2**. To a stirred solution of triflic anhydride (1.9 mL, 11.3 mmole) in CH_2Cl_2 (35 mL) under Ar at -75 °C was added a solution of 4-cyanobenzyl alcohol (**1**)(1.37g, 10.3 mmole) and diisopropylethylamine (1.97 mL, 11.3 mmole) in CH_2Cl_2 (12 mL) dropwise. Stirring at -78 °C was continued for 20 min. and a solution of N-Bis-Boc-histamine (3.2 g, 10.3 mmole) in CH_2Cl_2 (35 mL) was added. The reaction was allowed to warm to room temperature slowly and stirred overnight. The reaction mixture was washed with sat. Na_2CO_3 solution (30 mL). The organic phase was dried (Na_2SO_4) and solvent removed in vacuo. The residue was purified by column chromatography with 5 % MeOH in CH_2Cl_2 to give 1.38g product in 41% yield. MS: m/z 327 (MH^+). This compound was treated with 25% trifluoroacetic acid in CH_2Cl_2 (20 mL) for 1 h. Solvent was removed in vacuo. The residue was dissolved in 5% HCl (15 mL) and

washed with CH_2Cl_2 (10 mLx2). The aqueous layer was basified with NaOH to PH=9 and extracted with ethyl acetate (30 mLx 4). The combined organic phase was dried (Na_2SO_4) and solvent removed in vacuo to give 600 mg desired amine **2** in 66% yield. MS: m/z 227 (MH^+).

2. Preparation of compound **3**. To a stirred solution of the amine (**2**) (600 mg, 2.65 mmole) and N-4-Fmoc-N-1-Boc-piperazine carboxylic acid (1 g, 2.21mmole) in CH_2Cl_2 (20 mL) was added DCC (547 mg, 2.65 mmole) and HOBt (358 mg, 2.65 mmole). The reaction was stirred overnight. The reaction mixture was filtered. The filtrate was washed with water (20 mL). The organic phase was dried (Na_2SO_4) and solvent removed in vacuo. The residue was purified by flash column chromatography with 5% MeOH in CH_2Cl_2 to give the amide. The amide was treated with 20% piperidine in $CHCl_3$ (10 mL) for 2 h. Solvent was removed in vacuo. The residue was purified by column chromatography with 5 - 10% MeOH in CH_2Cl_2 to give 713 mg desired amine in 74% yield. MS: m/z 439 (MH^+).

3. Preparation of compound **4**. Amine **3** (40 mg, 0.09 mmole) was dissolved in MeOH (3 mL), cyclohexylacetaldehyde (23 μL, 0.18 mmole) and sodium cyanoborohydride (182 μL 1.0 M solution in THF, 0.18 mmole) was added. The reaction was stirred overnight. Solvent was removed in vacuo and the residue was purified by flash column chromatography with 3 - 5 % MeOH in CH_2Cl_2 to give 22 mg of desired product in 44% yield. MS: m/z 549 (MH^+).

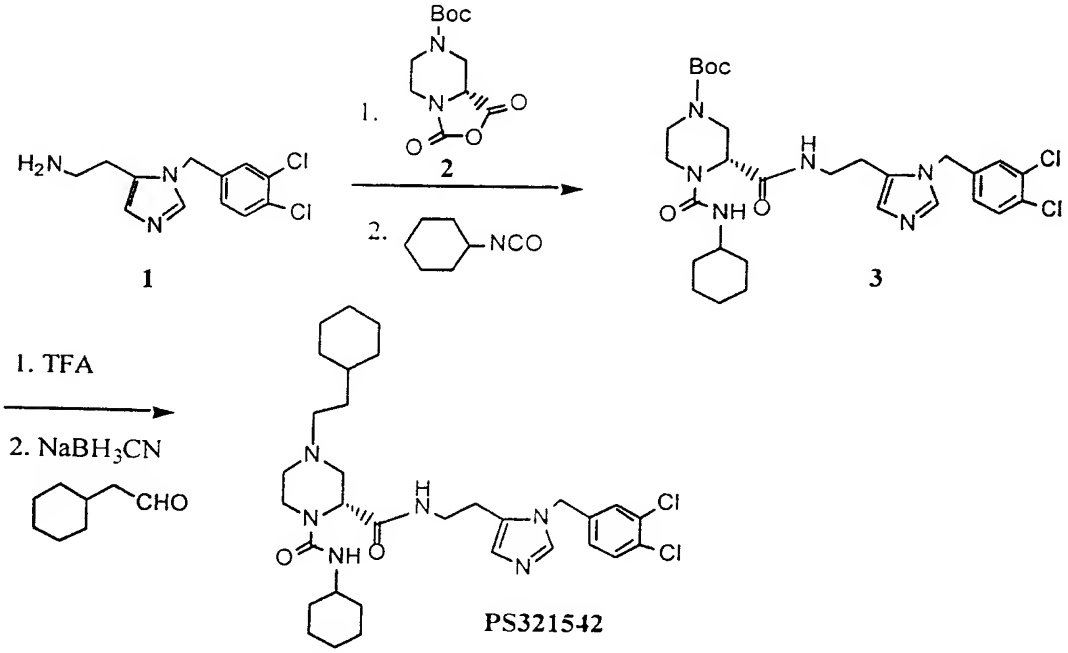
4. Preparation of PS461400. To a stirred solution of compound 4 (22 mg, 0.04 mmole) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (0.5 mL). The mixture was stirred for 1 h and solvent was removed in vacuo. The residue was pumped on a high vacuum line for 2 h and dissolved in CH_2Cl_2 (2 mL). To this solution was added diisopropylethyl amine (35 μL, 0.2 mmole) and the cyclohexyl isocyanate (28.5 uL, 0.2 mmole). The reaction was stirred overnight, dissolved in water (10 mL) and extracted with CH_2Cl_2 (15 mL x 2). The organic layer was dried (Na_2SO_4) and solvent was removed in

vacuo. The residue was purified by flash column chromatography with 4% MeOH in CH_2Cl_2 to give 11 mg desired product in 48% yield. MS: m/z 574 (MH^+).

Using substantially the same reaction scheme of the above example, with appropriate alcohol **1**, the following compounds were prepared:

PS287238	PS812520	PS465781	PS159773	PS372802
PS793961	PS478500	PS783003	PS593455	PS320451
PS477090	PS516972	PS410892	PS241936	PS409643
PS725556	PS769295	PS075114	PS990951	PS192638
PS354164	PS395570	PS956973	PS859989	PS467023

Scheme 3



Preparation procedure for PS 321542 (Scheme 3)

1. Preparation of compound **3**. To a stirred solution of the anhydride **1** (100 mg, 0.39 mmole) in CH_2Cl_2 (4 mL) was added a solution of the amine **1** (105 mg, 0.39 mmole) in a mixture of MeOH/CH_2Cl_2(0.5 mL/2 mL). The reaction was stirred for 1 h. The reaction was cooled to 0 °C and

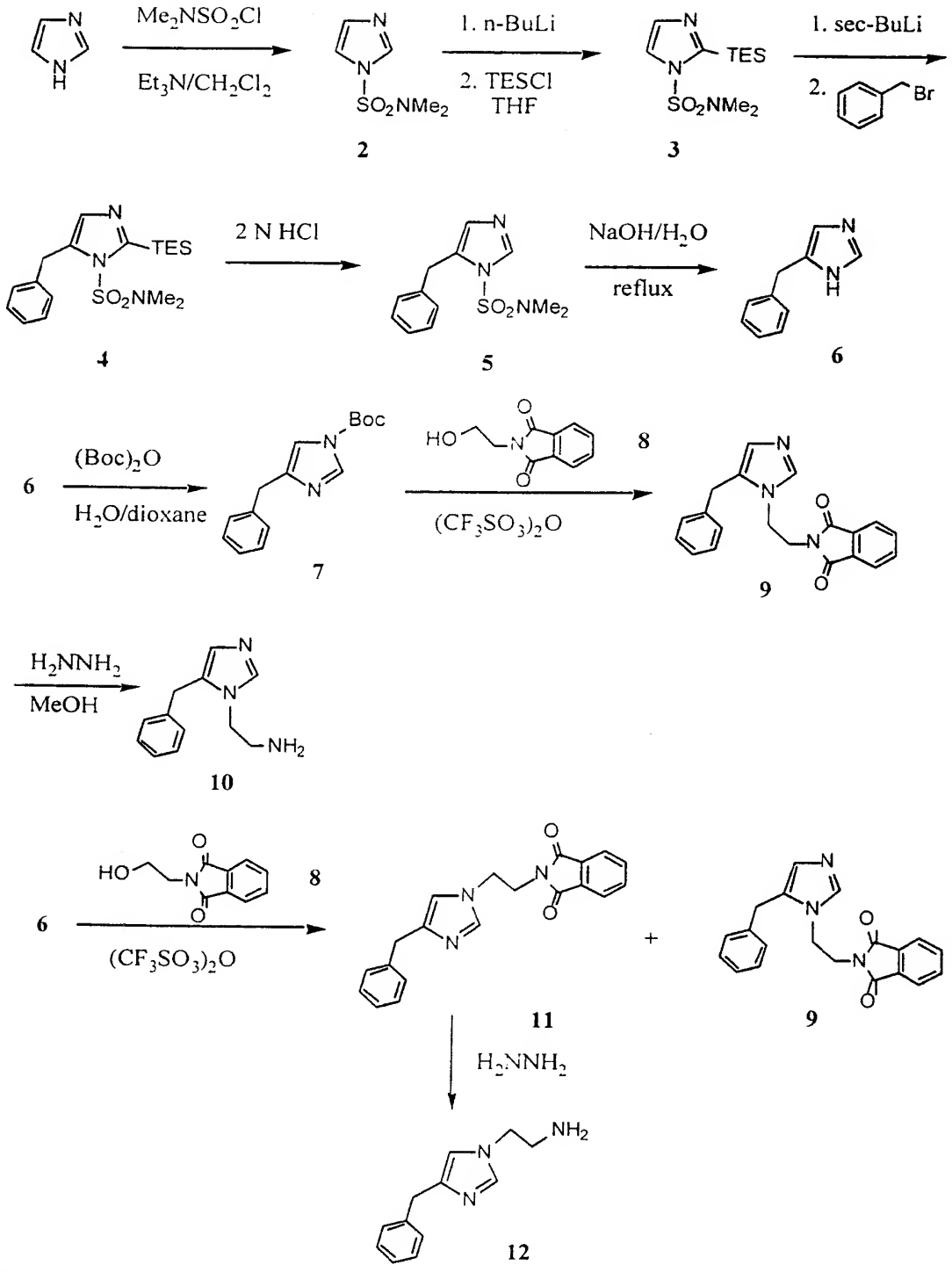
cyclohexyl isocyanate (111 μL, 0.78 mmole) was added. The reaction was stirred overnight. The reaction was partitioned between CH_2Cl_2 (40 mL) and sat. NaCl solution (20 mL). The organic layer was dried (Na_2SO_4) and solvent removed in vacuo to give 200 mg desired product in 85% yield. MS: m/z 607 (MH^+).

2. Preparation of compound PS321542. To a stirred solution of compound **3** (137 mg, 0.226 mmole) in CH_2Cl_2 (3 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 1 h and solvent was removed in vacuo. The residue partitioned between 1 N NaOH (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 and EtOAc. The combined organic phase was dried (Na_2SO_4) and solvent was removed in vacuo. The amine was dissolved in MeOH (3 mL). To this solution was added cyclohexyl acetaldehyde (57 mg, 0.45 mmole) and sodium cyanoborohydride (1.0 M solution in THF, 452 μL, 0.45 mmole). The reaction was stirred overnight. Solvent was removed in vacuo and the residue partitioned between 1 N NaOH (20 mL) and CH_2Cl_2 (20 mL). The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography with 4% MeOH in CH_2Cl_2 to give 52 mg product in 37% yield. MS: m/z 617 (M^+).

Using substantially the same reaction scheme of the above example, with racemic anhydride **2** when appropriate, the following compounds were prepared:

PS 815156	PS288326	PS130057	PS064691	PS028348
PS813558	PS319448	PS420083	PS259236	PS437810
PS381385	PS201633			

Scheme 4



Preparation procedure for 1-(2-Aminoethyl)-5-benzylimidazole (10) and 1-(2-Aminoethyl)-4-benzylimidazole (12) (Scheme 4)

1. Preparation of compound **2**. To a stirred solution of imidazole (5g, 73.4 mmole) in CH_2Cl_2 (30 mL) at 0 °C was added triethylamine (15.4 mL, 110 mmole) and dimethylsulfamoyl chloride (8.3 mL, 77.1 mmole) dropwise. The reaction was allowed to warm to room temperature slowly and stirred overnight. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (30 mLx2). The organic phase was dried (Na_2SO_4) and solvent removed in vacuo to give compound **2** in 89% yield. MS: m/z 176 (MH^+).

2. Preparation of compound **5**. To a stirred solution of compound **2** (1.0g, 5.72 mmole) in THF (20 mL) at -78 °C under Ar was added n-BuLi in hexane (2.5 M solution, 2.44 mL, 6.12 mmole). The reaction mixture was stirred at at -78 °C for 30 min., and chlorotriethylsilane (1.92 mL, 11.44 mmole) was added. The reaction was stirred at room temperature for 5 h, then solvent and excess chlorosilane was removed under reduced pressure by gentle heating to give intermediate **3**. THF (20 mL) was added to intermediate **3** and the solution was cooled to -78 °C. Sec-butyllithium in cyclohexane (1.3 M solution, 8.8 mL, 11.44 mmole) was added and the mixture stirred at -78 °C for 30 min., then benzyl bromide (2.04 mL, 17.16 mmole) was added. Stirring was continued at -78 °C for 30 min., and at room temperature overnight. Solvent was removed in vacuo to give intermediate **4**. Intermediate **4** was stirred with 2 N HCl (50 mL) for 3 h and the mixture was washed with ether (20 mLx2). The aqueous phase was basified with NaOH (40% w/w) to pH=11, then extracted with ether (50 mLx3). Combined organic phase was dried (Na_2SO_4) and solvent removed in vacuo. The residue was purified by flash column chromatography with 35% hexane in EtOAc to give 560 mg compound **5** in 37% yield. MS: m/z 266 (MH^+).

3. Preparation of compound **6**. Compound **5** (560 mg, 2.11 mmole) was refluxed in 4% NaOH (w/w, 100 mL) overnight. Solvent was removed in vacuo. The residue was triturated with THF, filtered and dried (Na_2SO_4).

Solvent was removed under reduced pressure to give 240 mg 4(5)-benzylimidazole (**6**) in 72% yield. MS: m/z 159 (MH^+).

4. Preparation of 1-(2-Aminoethyl)-5-benzylimidazole **(10)**. To a stirred solution of compound **6** (230 mg, 1.45 mmole) in H_2O/dioxane (1:1, 20 mL) was added sodium carbonate (31 mg, 0.29 mmole) and di-t-butyl-dicarbonate (400 mg, 1.74 mmole). The mixture was stirred overnight, then extracted with CH_2Cl_2 (40 mL x 2). Combined organic layer was washed with water (20 mL), dried (Na_2SO_4) and solvent was removed in vacuo to give 305 mg compound **7** in 82% yield. MS: m/z 259 (MH^+). To a stirred solution of triflic anhydride (219 μL, 1.3 mmole) in CH_2Cl_2 (5 mL) under Ar at -78 °C was added a solution of compound **8** (249 mg, 1.3 mmole) and DIEA in CH_2Cl_2 (5 mL). Stirring at -78 °C was continued for 20 min., a solution of compound **7** in CH_2Cl_2 (5 mL) was added dropwise. The reaction was allowed to gradually warm to room temperature overnight. To the reaction was added sat. $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (20 mL x 2). Organic layer was washed with water (10 mL), dried (Na_2SO_4) and solvent removed in vacuo. The residue was purified by column chromatography with 1-5 % MeOH in CH_2Cl_2 to give 60 mg compound **9**. MS: m/z 332 (MH^+). Compound **9** was dissolved in MeOH (2 mL) and hydrazine (10 μL) was added. The reaction was stirred overnight and solvent was removed in vacuo. The residue was dissolved in 0.1 N HCl (10 mL) and washed with EtOAc (10 mL). The aqueous phase was basified with NaOH until pH=11, and extracted with EtOAc (20 mLx3). Combined organic layer was dried (Na_2SO_4) and solvent removed in vacuo to give the title compound **10**. MS: m/z 202 (MH^+).

5. Preparation of 1-(2-Aminoethyl)-4-benzylimidazole **(12)**. To a stirred solution of triflic anhydride (245 μL, 1.46 mmole) in CH_2Cl_2 (5 mL) under Ar at -78 °C was added a solution of compound **8** (278 mg, 1.46 mmole) and DIEA in CH_2Cl_2 (5 mL). Stirring at -78 °C was continued for 20 min., a solution of compound **6** in CH_2Cl_2 (5 mL) was added dropwise. The

reaction was allowed to gradually warm to room temperature overnight. To the reaction was added sat. $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (20 mL x 2). Organic layer was washed with water (10 mL), dried (Na_2SO_4) and solvent removed in vacuo. The residue was purified by column chromatography with 1-5 % MeOH in CH_2Cl_2 to give 112 mg compound **11**. MS: m/z 332 (MH^+). Compound **11** was dissolved in MeOH (2 mL) and hydrazine (10 μL) was added. The reaction was stirred overnight and solvent was removed in vacuo. The residue was dissolved in 0.1 N HCl (10 mL) and washed with EtOAc (10 mL). The aqueous phase was basified with NaOH until pH=11, and extracted with EtOAc (20 mLx3). Combined organic layer was dried (Na_2SO_4) and solvent removed in vacuo to give the title compound **12**. MS: m/z 202 (MH^+).

Compound **10** was used to prepare PS319448 using procedure described in **scheme 2**. Compound **12** was used to prepare PS204446 using procedure described in **scheme 2**.

Reagents and reaction conditions for protecting and deprotecting compounds is well known, as described, for example, in T.W. Greene and P. Wuts, Protective Groups in Organic Synthesis, 2nd Ed., Wiley Interscience, N.Y. 1991, 473 pages.

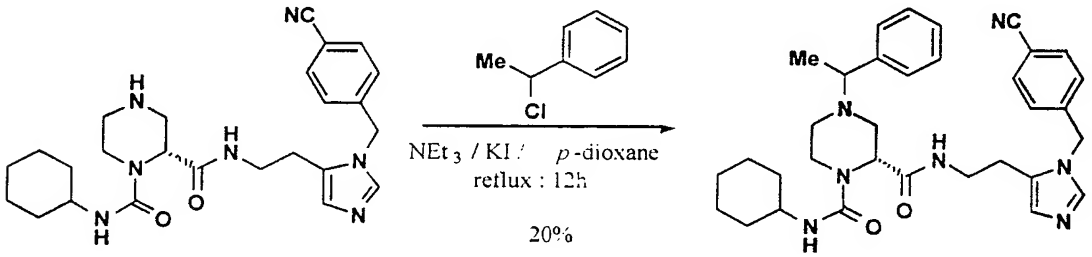
Compounds of the present invention and preparative starting materials therof, are exemplified by the following examples, which should not be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art, such as by the methods described in WO95/10516.

Compounds of formula (1.0) can be isolated from the reaction mixture using conventional procedures, such as, for example, extraction of the reaction mixture from water with organic solvents, evaporation of the organic solvents, followed by chromatography on silica gel or other suitable chromatographic media. Alternatively, compounds (1.0) can be dissolved in a water-miscible solvent, such as methanol, the methanol solution is

added to water to precipitate the compound, and the precipitate is isolated by filtration or centrifugation.

Compounds of the present invention and preparative starting materials thereof, are exemplified by the following examples, which should not be construed as limiting the scope of the disclosure.

Example 1.



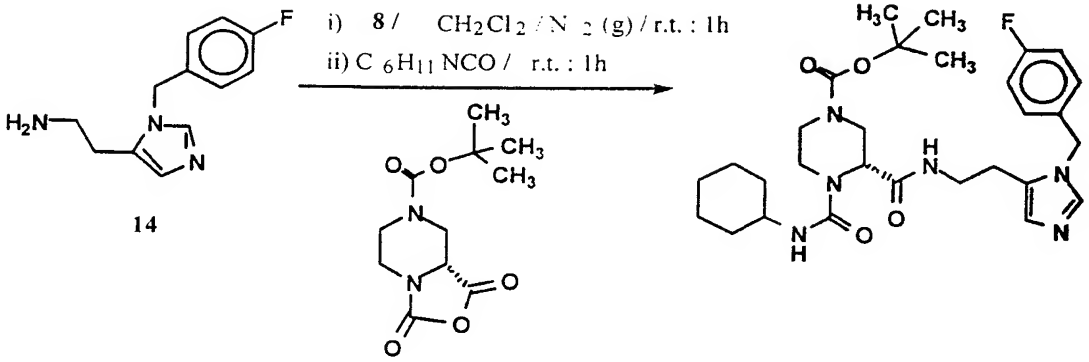
10

A solution of **10** (50 mg, 0.108 mmol, 1.0 eq.), 1-chloro-1-phenylethane (170 µl, 1.29 mmol, 12.0 eq.), and triethylamine (180 µl, 1.29 mmol, 12.0 eq.) in anhydrous *p*-dioxane (10 ml) is gently refluxed at 105 °C under a nitrogen atmosphere for 12h. The solution is cooled to room temperature and the volatiles are removed under vacuum at 30 °C. The residue is taken up in distilled water (10 ml) and extracted with dichloromethane (5 x 5 ml). The combined organic extracts are washed with brine (5 ml), dried over Na_2SO_4, filtered, and concentrated under vacuum at 30 °C. *N2-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-N1-cyclohexyl-4-(1-phenylethyl)-1,2(R)-piperazinedicarboxamide* (12 mg, 0.021 mmol, 20%) is obtained as a light-yellow semi-solid after preparative scale thin layer chromatography (CH_3CN : 2 *N* NH_3 / MeOH = 90 : 10 v/v as eluent) over silica gel.

HR-MS (FAB):

Calculated for $C_{33}H_{42}N_7O_2$ ([M+H]$^+$): 568.3400. Found: 568.3407.

Example 2.



14

8

A solution of **14** (500 mg, 2.28 mmol, 1.0 eq.) in anhydrous dichloromethane (5 ml) was added dropwise over a period of 5 minutes to a stirred solution of anhydride **8** (701 mg, 2.74 mmol, 1.2 eq.) in anhydrous dichloromethane (10 ml) at room temperature. A stream of nitrogen was bubbled through the solution to expel evolved carbon dioxide. The colorless solution was stirred for one hour amid nitrogen bubbling. Bubbling was terminated and cyclohexyl isocyanate (594 ml, 4.56 mmol, 2.0 eq.) was added dropwise over a period of 5 minutes. The light-yellow solution was stirred at room temperature for one hour. The volatiles were removed under vacuum at 30 °C. The resulting viscous oil was partitioned between dichloromethane (25 ml) and 1 *N* aqueous NaOH solution (25 ml). The aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic extracts were washed with brine (5 ml), dried over Na_2SO_4, filtered, and concentrated under vacuum at 30 °C. Preparative scale thin layer chromatography (CH_2Cl_2 : 2 *N* NH_3 / MeOH = 90 : 10 v/v) over silica gel afforded *1,1-dimethylethyl-1-[(cyclohexylamino)carbonyl]-2(R)-[[[2-[1-(4-fluorophenyl)methyl]-1H-imidazol-5-yl]ethyl]amino]carbonyl]-4-piperazinecarboxylate* (190 mg, 0.34 mmol, 15%) as an off-white foam.

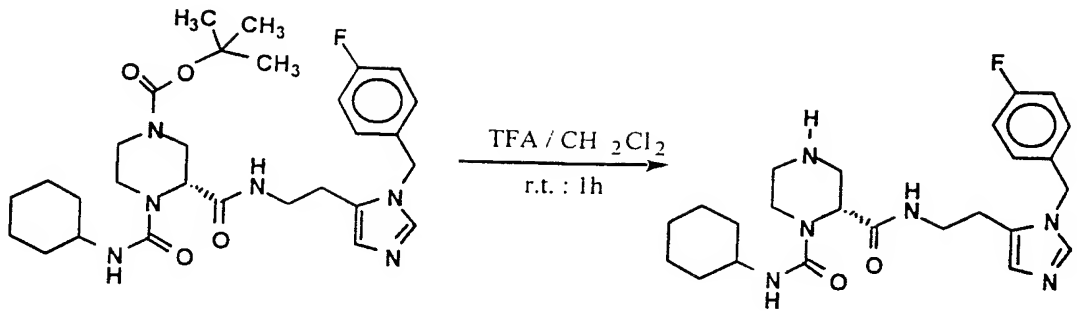
Melting Point: 72 °C (decomposition).

MS (FAB+): m/e 557 ($[M+H]^+$).

HR-MS (FAB):

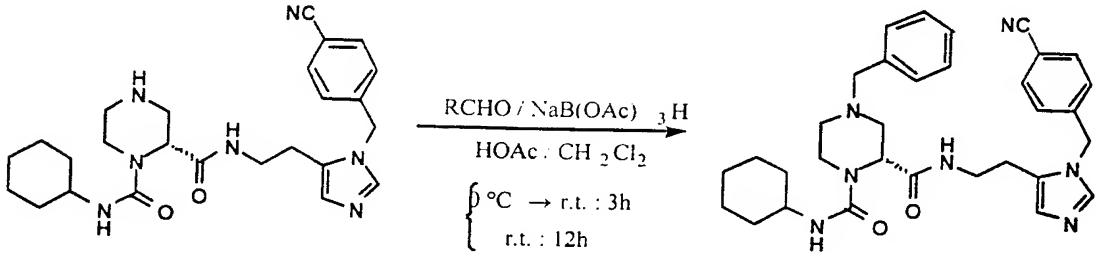
Calculated for $C_{29}H_{42}FN_6O_4$ ($[M+H]^+$): 557.3252. Found: 557.3240.

Example 3.



The title compound of Example 2 (190 mg, 0.34 mmol, 1.0 eq.) was dissolved in a mixture of anhydrous dichloromethane (10 ml) and trifluoroacetic acid (10 ml). The resulting yellow solution was stirred at ambient temperature under a nitrogen atmosphere for one hour. The volatiles were evaporated under vacuum at 30 °C and the remaining viscous oil was directly flash chromatographed (CH_2Cl_2 : 2 *N* NH_3 / MeOH = 90 : 10 v/v) over silica gel to give *N2-[2-[1-[(4-fluorophenyl)methyl]-1H-imidazol-5-yl]ethyl]-N1-cyclohexyl-1,2(R)-piperazinecarboxamide* (121 mg, 0.27 mmol, 78%) as an off-white solid.

Example 4.



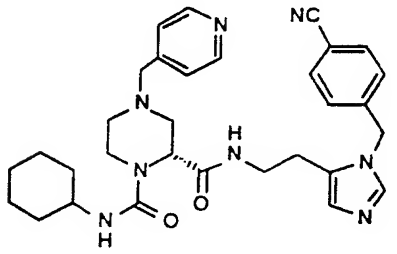
10 11

Sodium triacetoxyborohydride (75 mg, 0.336 mmol, 3.1 eq.) is added portionwise (3 x 25 mg) to a stirred solution of **10** (50 mg, 0.108 mmol, 1.0 eq.) and benzoic aldehyde (R=phenyl) (0.336 mmol, 3.1 eq.) in a mixture of glacial acetic acid (0.5 ml) and anhydrous dichloromethane (10 ml) at 0 °C under a nitrogen atmosphere. The mixture is slowly (3h) warmed to room temperature and stirred for another 12h. The volatiles are removed under vacuum at 30 °C. The residue is taken up in 1 *N* aqueous NaOH solution (10 ml) and extracted with dichloromethane (5 x 5 ml). The

combined organic extracts are washed with brine (5 ml), dried over Na_2SO_4, filtered, and concentrated under vacuum at 25 °C. The product is obtained after preparative scale thin layer chromatography (using either CH_2Cl_2 : 2 *N* NH_3 / MeOH = 90 : 10 v/v or CH_3CN : 2 *N* NH_3 / MeOH = 90 : 10 v/v as eluent) over silica gel.

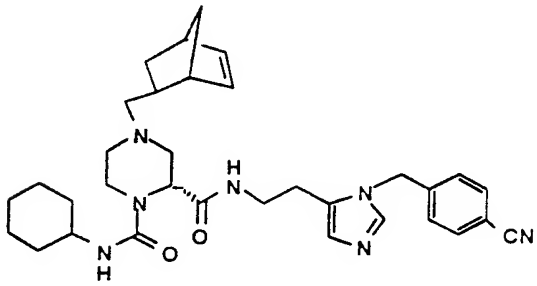
In Examples 5-28 by following essentially the same procedure as described in Example 4, except that the corresponding aldehyde is substituted for benzoic aldehyde, the title compound is obtained.

Example 5.



Decomposition point: 80°C

Example 6.



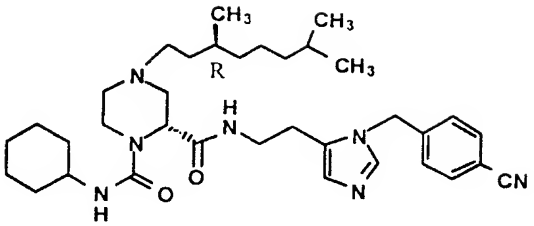
Decomposition point: semi-solid

Accurate Mass ([M+H]$^+$)

Calculated: 570.3556.

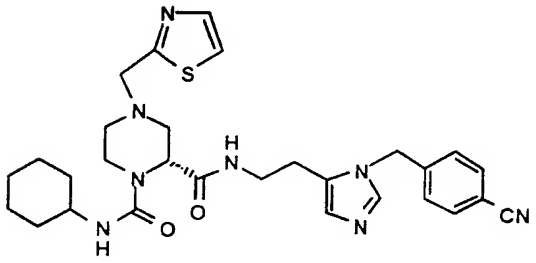
Found: 570.3570.

Example 7.



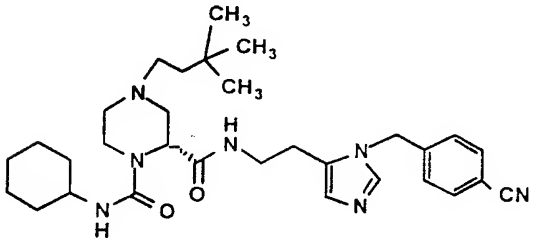
Decomposition point: 90°C
Accurate Mass ([M+H]$^+$)
Calculated: 504.4339.
Found: 504.4313.

Example 8.



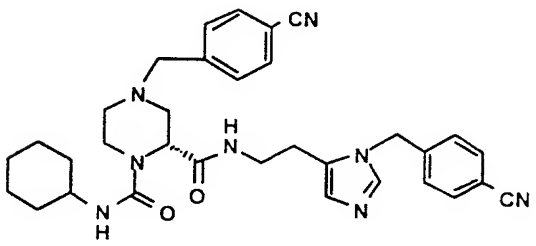
Decomposition point: 85°C
Accurate Mass ([M+H]$^+$)
Calculated: 561.2760.
Found: 561.2755.

Example 9



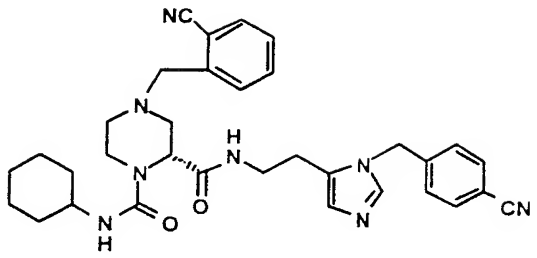
Decomposition point: 65°C
Accurate Mass ([M+H]$^+$)
Calculated: 548.3713.
Found: 548.3712.

Example 10.



Decomposition point: 155°C
Accurate Mass ([M+H]$^+$)
Calculated: 579.3196.
Found: 579.3200.

Example 11.



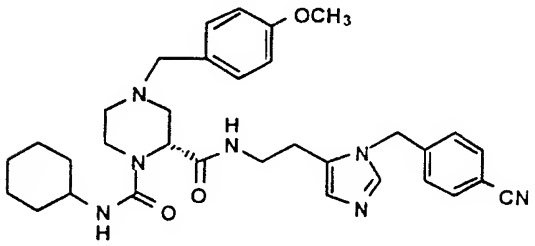
Decomposition point: 95°C

Accurate Mass ([M+H]$^+$)

Calculated: 579.3196.

Found: 579.3189.

Example 12



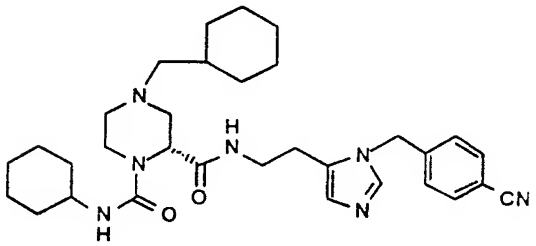
Decomposition point: oil

Accurate Mass ([M+H]$^+$)

Calculated: 584.3349.

Found: 584.3352.

Example 13.



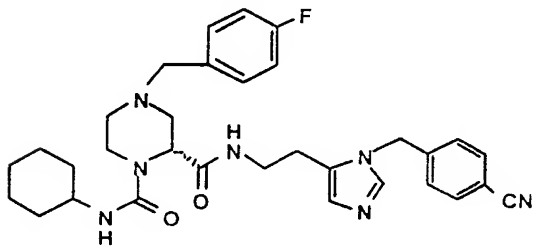
Decomposition point: semi-solid

Accurate Mass ([M+H]$^+$)

Calculated: 560.3713.

Found: 560.3712.

Example 14.



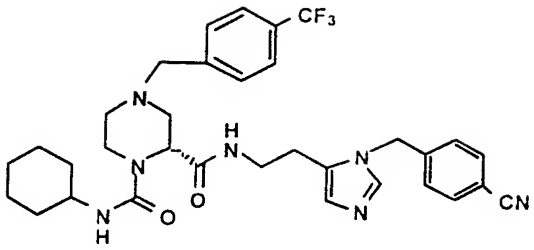
Decomposition point: semi-solid

Accurate Mass ([M+H]$^+$)

Calculated: 572.3149.

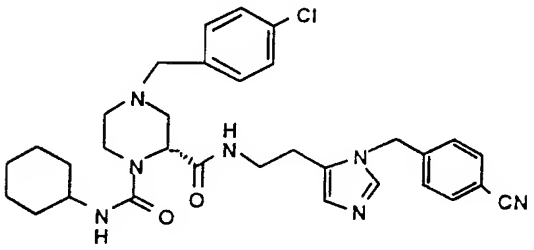
Found: 572.3145.

Example 15.



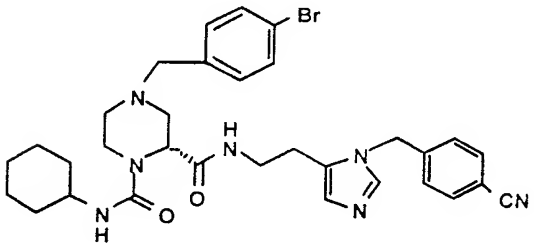
Decomposition point: 165°C
Accurate Mass ([M+H]$^+$)
Calculated: 622.3117.
Found: 622.3134.

Example 16.



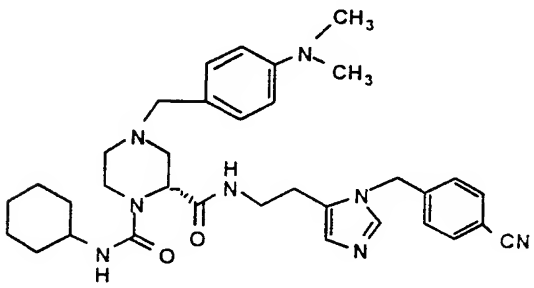
Decomposition point: 180°C
Accurate Mass ([M+H]$^+$)
Calculated: 588.2854.
Found: 588.2850.

Example 17.



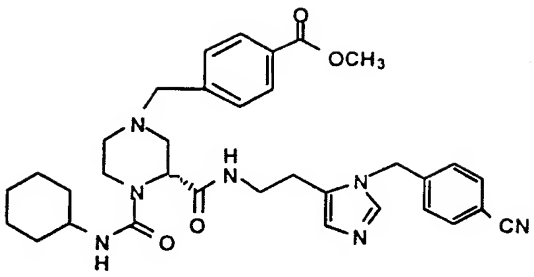
Decomposition point: semi-solid
Accurate Mass ([M+H]$^+$)
Calculated: 632.2349.
Found: 632.2334.

Example 18.



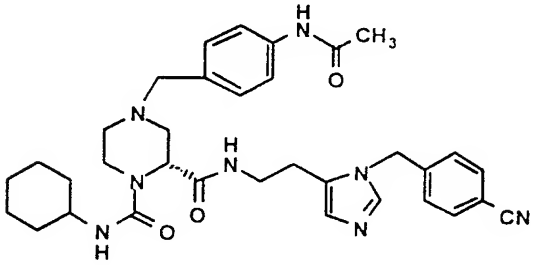
Decomposition point: oil
Accurate Mass ([M+H]$^+$)
Calculated: 597.3665.
Found: 597.3653.

Example 19.



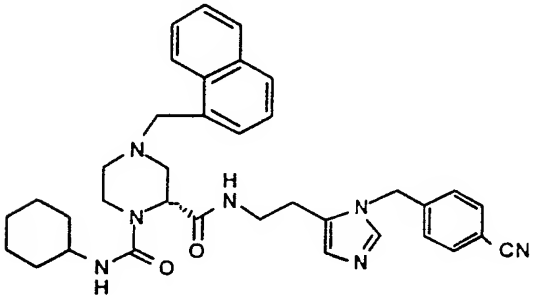
Decomposition point: 205°C
Accurate Mass ([M+H]$^+$)
Calculated: 612.3298.
Found: 612.3308.

Example 20.



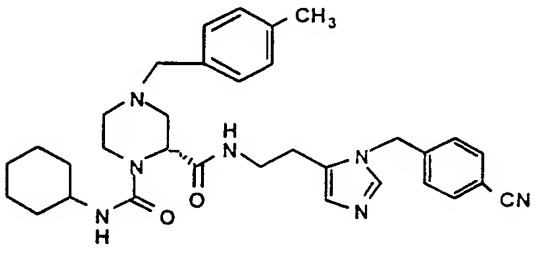
Decomposition point: 120°C
Accurate Mass ([M+H]$^+$)
Calculated: 611.3458.
Found: 611.3474.

Example 21.



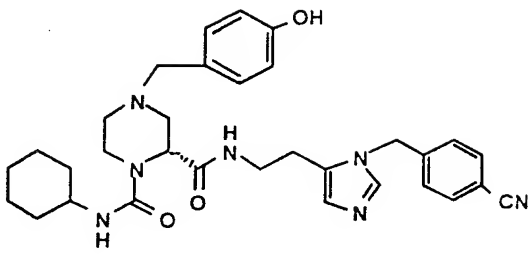
Decomposition point: 100°C
Accurate Mass ([M+H]$^+$)
Calculated: 611.3400.
Found: 611.3424.

Example 22.



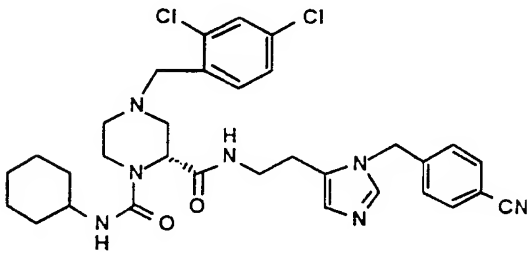
Decomposition point: 185°C
Accurate Mass ([M+H]$^+$)
Calculated: 568.3400.
Found: 568.3410.

Example 23.



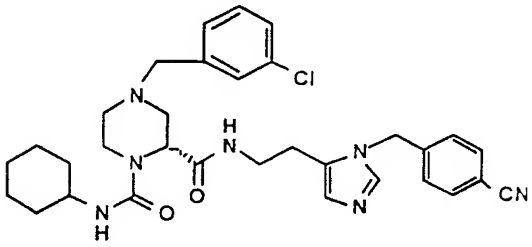
Decomposition point: semi-solid
Accurate Mass ([M+H]$^+$)
Calculated: 570.3193.
Found: 570.3194.

Example 24.



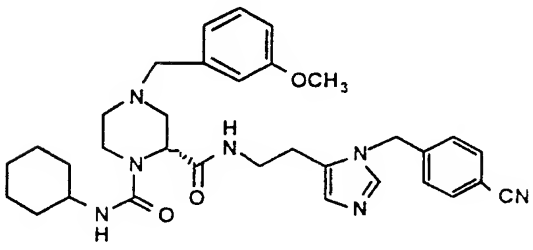
Decomposition point: 185°C
Accurate Mass ([M+H]$^+$)
Calculated: 622.2464.
Found: 622.2452.

Example 25.



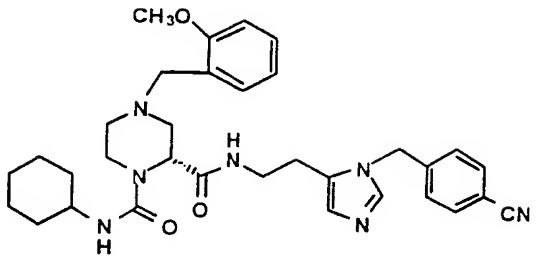
Decomposition point: 130°C
Accurate Mass ([M+H]$^+$)
Calculated: 588.2854.
Found: 588.2857.

Example 26.



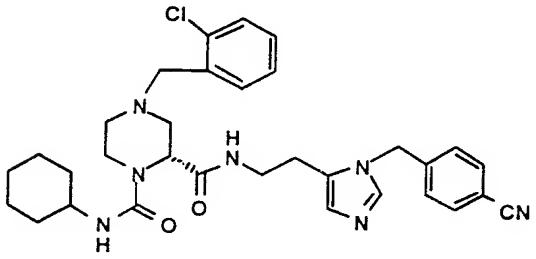
Decomposition point: 160°C
Accurate Mass ([M+H]$^+$)
Calculated: 584.3349.
Found: 584.3347.

Example 27.



Decomposition point: 130°C
Accurate Mass ([M+H]$^+$)
Calculated: 584.3349.
Found: 584.3356.

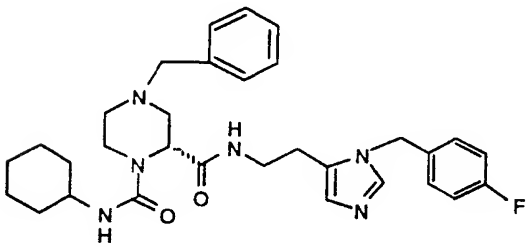
Example 28.



Decomposition point: 110°C
Accurate Mass ([M+H]$^+$)
Calculated: 588.2854.
Found: 588.2844.

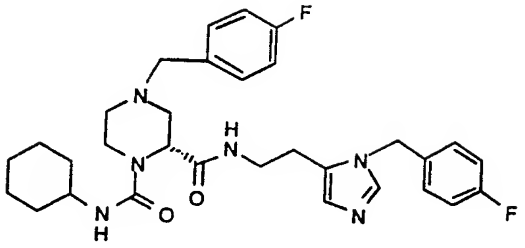
By using the title compounds of Example 3 and by following essentially the same procedure as described in Example 4, the following compounds are prepared.

Example 28A.



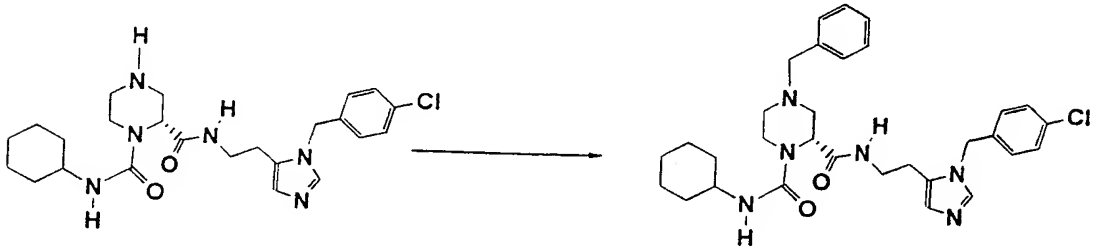
Decomposition point: 155°C
Accurate Mass ([M+H]$^+$)
Calculated: 547.3197
Found: 547.3192

Example 28B.



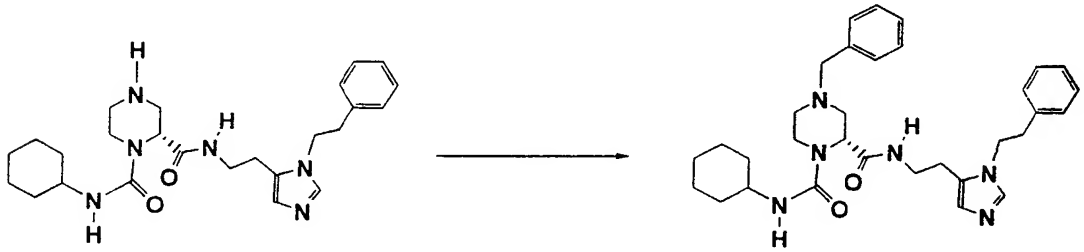
Decomposition point: 165°C
Accurate Mass ([M+H]$^+$)
Calculated: 565.3103
Found: 565.3106

Example 28C. N4-phenylmethyl-N2-[2-[1-[(4-chlorophenyl)methyl]-1H-imidazol-5-yl]ethyl]-N1-cyclohexyl-1,2(R)-piperazinedicarboxamide



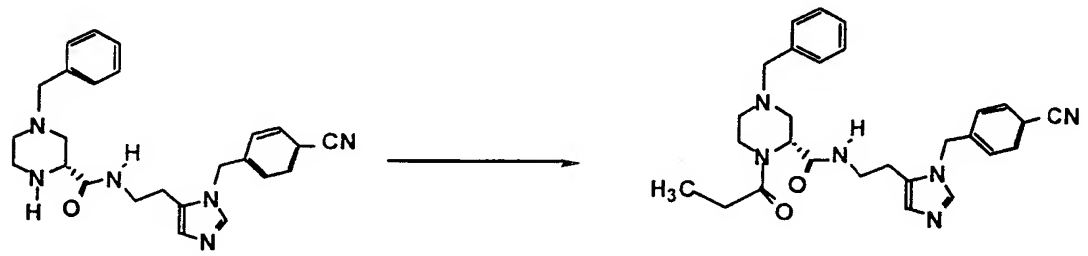
To the title compound from Preparative Example 12 (75 mg, 0.16 mmol) and benzaldehyde (0.05 mL, 0.5 mmol) dissolved in glacial acetic acid (0.5 mL) and anhydrous dichloromethane (10 ml) at 0°C is added sodium triacetoxyborohydride (102 mg, 0.5 mmol) and the resulting mixture is warmed to room temperature and stirred for an additional 12 hours. The reaction mixture is concentrated *in vacuo*, diluted with dichloromethane and washed with 1*N* NaOH (aq). The organic phase is dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and purified by preparative plate chromatography (silica gel) using 7% MeOH (saturated with ammonia 2*M*)-CH_3CN as eluent to afford the title compound as a white solid (60 mg, MH^+ = 563, mp = 116.2°C).

Example 28D. N4-phenylmethyl-N2-[2-[1-(phenylethyl)-1H-imidazol-5-yl]ethyl]-N1-cyclohexyl-1,2(R)-piperazinedicarboxamide



To the title compound from Preparative Example 12A (75 mg, 0.17 mmol) and benzaldehyde (0.05 mL, 0.5 mmol) dissolved in glacial acetic acid (0.5 mL) and anhydrous dichloromethane (10 ml) at 0°C is added sodium triacetoxyborohydride (108 mg, 0.5 mmol) and the resulting mixture is warmed to room temperature and stirred for an additional 12 h. The reaction mixture is concentrated *in vacuo*, diluted with dichloromethane and washed with 1*N* NaOH (aq). The organic phase is dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and purified by preparative plate chromatography (silica gel) using 7% MeOH (saturated with ammonia 2*M*)-CH_3CN as eluent to afford the title compound as a white solid (61 mg, MH^+ = 543, mp = 64.4°C).

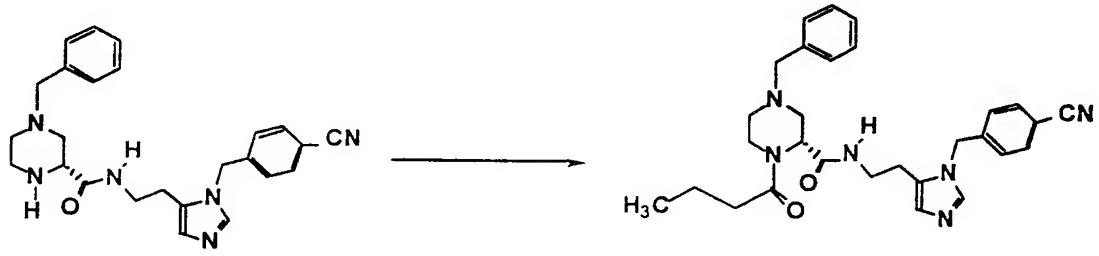
Example 28E. N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-1-(1-oxopropyl)-4-phenyl(methyl)-2(R)-piperazinedicarboxamide



To a solution of the title compound from Preparative Example 11 (50 mg, 0.12 mmol, 1.0 eq) and triethylamine (33 mL, 0.24 mmol) in anhydrous dichloromethane (2 ml) is added propionyl chloride (15.2 mL, 0.18 mmol). The resulting mixture is stirred at room temperature under N_2 for 48 hrs and then quenched with saturated $NaHCO_3$(aq) solution. The mixture is extracted with dichloromethane and dried over anhydrous Na_2SO_4. The

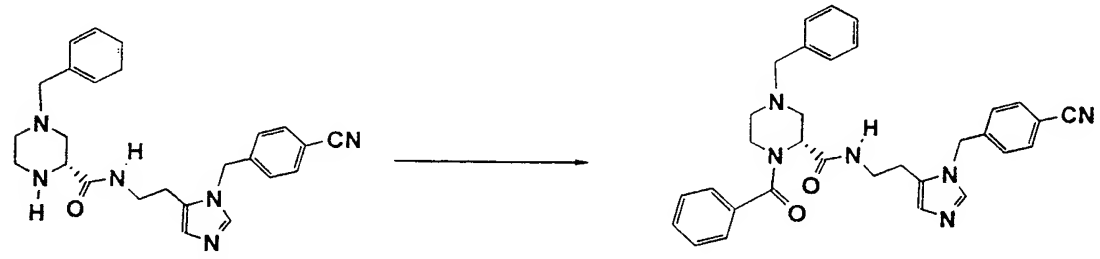
organic phase is filtered, concentrated in vacuo, and the residue purified by preparative plate chromatography (silica gel) using 6% methanol - dichloromethane saturated with ammonium hydroxide to afford the title compound as an off-white solid (38.1 mg, mp = 88.2-168.6°C, MH+ = 485).

Example 28 F. N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-1-(1-oxobutyl)-4-phenyl(methyl)-2(R)-piperazinedicarboxamide



In a similar manner as is described in Example 28E, but using butyryl chloride instead of propionyl chloride, the title compound is prepared as an off-white solid (34.3 mg, mp = 82.32-142.5°C, MH+ = 499).

Example 28G. 1-benzoyl-N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-4-phenylmethyl-2(R)-piperazinedicarboxamide



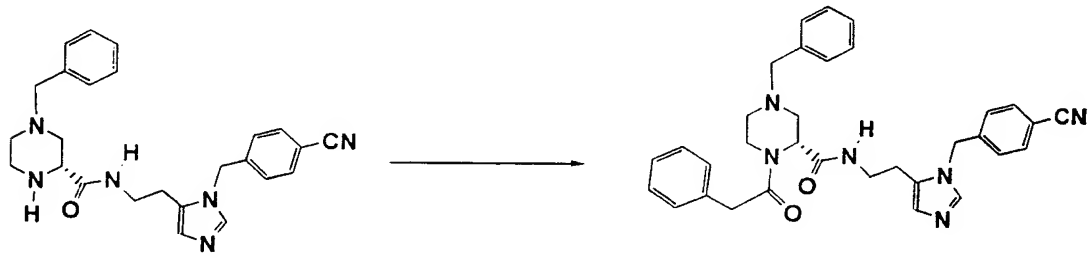
In a similar manner as is described in Example 28E, but using benzoyl chloride instead of propionyl chloride, the title compound is prepared as an off-white solid (33.2 mg, mp = 115.3-170.3°C, MH+ = 533).

Example 28H. 1-Acetyl-N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-4-(phenylmethyl)-2(R)-

piperazinedicarboxamide

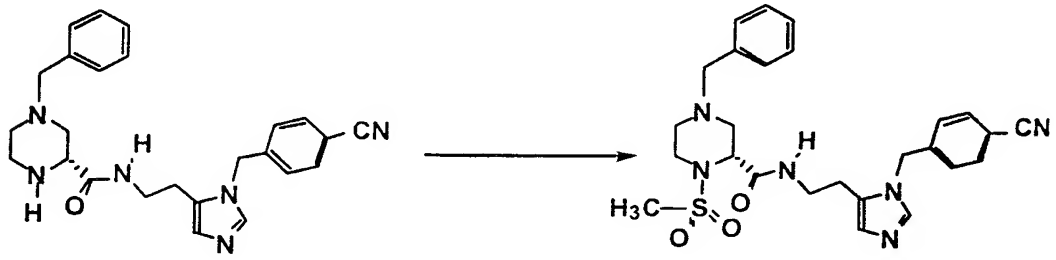
In a similar manner as is described in Example 28E, but using acetyl chloride instead of propionyl chloride, the title compound is prepared as an off-white solid (44.0 mg, mp = 93.0-174.9°C, MH+ = 471).

Example 28I. N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-1-phenylacetyl-4-(phenylmethyl)-2(R)-piperazinedicarboxamide



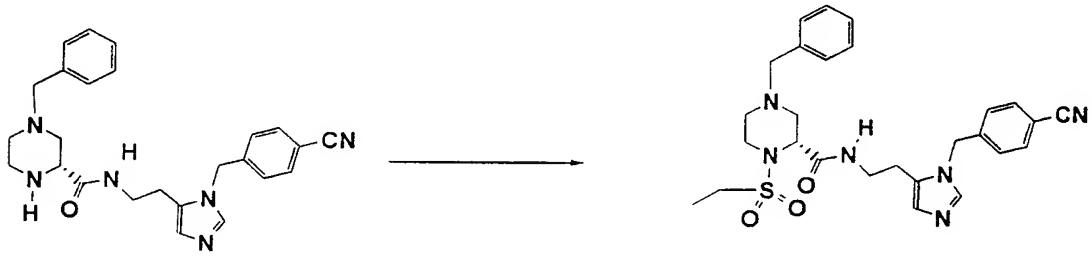
In a similar manner as is described in Example 28, but using phenylacetyl chloride instead of propionyl chloride, the title compound was prepared as an off-white solid (57.7 mg, 45%, mp = 85.6-96.7°C, MH+ = 547).

Example 28J. N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-1-(methylsulfonyl)-4-(phenylmethyl)-2(R)- piperazinecarboxamide



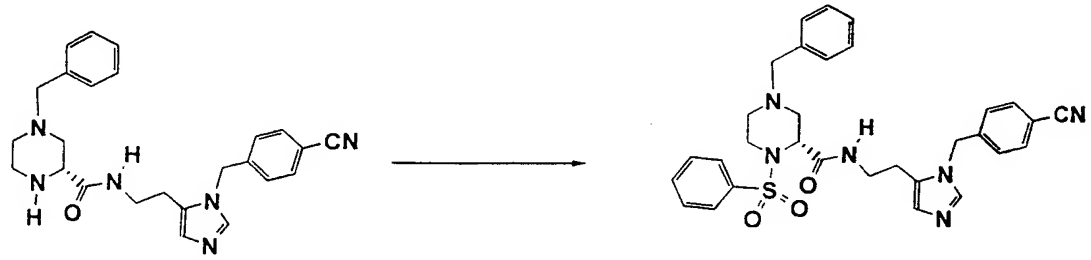
In a similar manner as described in Example 28E, but using methanesulfonyl chloride instead of propionyl chloride, the title compound is prepared as an off-white solid (52.4 mg, mp = 96.5-161.7°C, MH+ = 507).

Example 28K. N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-1-(ethylsulfonyl)-4-(phenylmethyl)-2(R)-piperazinecarboxamide



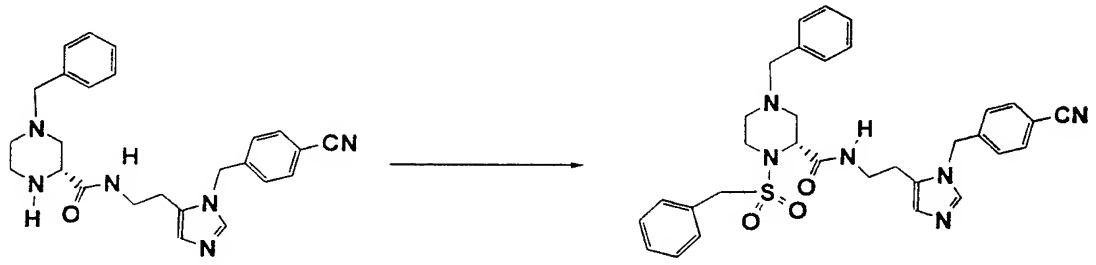
In a similar manner as is described in Example 28E, but using ethanesulfonyl chloride instead of propionyl chloride, the title compound is prepared as an off-white solid (40.4 mg, mp = 97.3-150.2°C, MH+ = 521).

Example 28L. N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-1-(phenylsulfonyl)-4-(phenylmethyl)-2(R)- piperazinecarboxamide



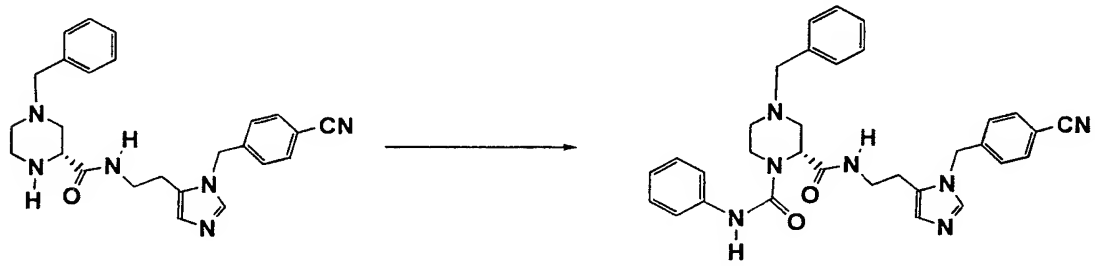
In a similar manner as is described in Example 28E, but using benzenesulfonyl chloride instead of propionyl chloride, the title compound is prepared as an off-white solid (50 mg, 75%, mp = 105.7-166.5°C, MH+ = 569).

Example 28M. N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-1-[(phenylmethyl)sulfonyl]-4-(phenylmethyl)-2(R)-piperazinecarboxamide



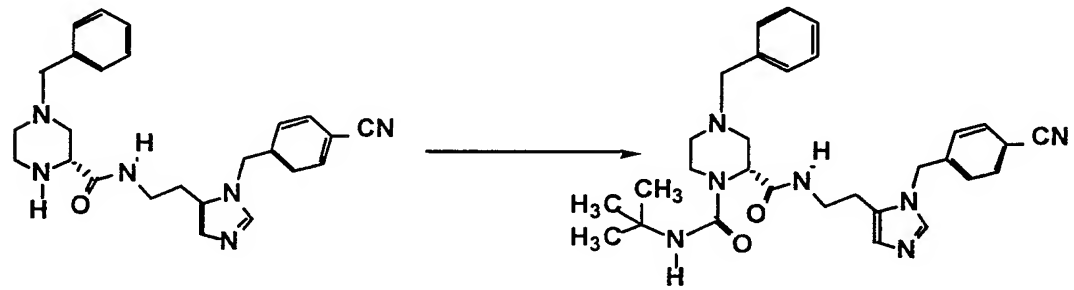
In a similar manner as is described in Example 28E, but using benzylsulfonyl chloride instead of propionyl chloride, the title compound is prepared as an off-white solid (26.8 mg, mp = 118.1-180.5°C, MH+ = 583).

Example 28N. N2-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-N1-phenyl-4-(phenylmethyl)-1,2(R)- piperazinecarboxamide



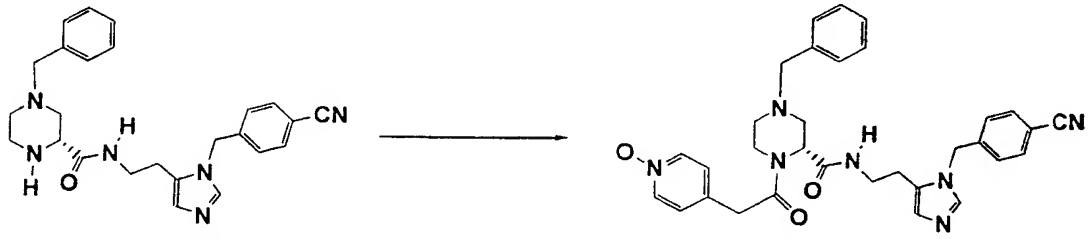
In a similar manner as is described in Preparative Example 12, but using the title compound from Preparative Example 11 and phenylisocyanate instead of cyclohexylisocyanate, the title compound is prepared as an off-white solid (28.8 mg, mp = 128.0-139.2°C, MH+ = 548).

Example 28O. N2-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-N1-(1,1-dimethylethyl)-4-(phenylmethyl)-1,2(R)-piperazinedicarboxamide



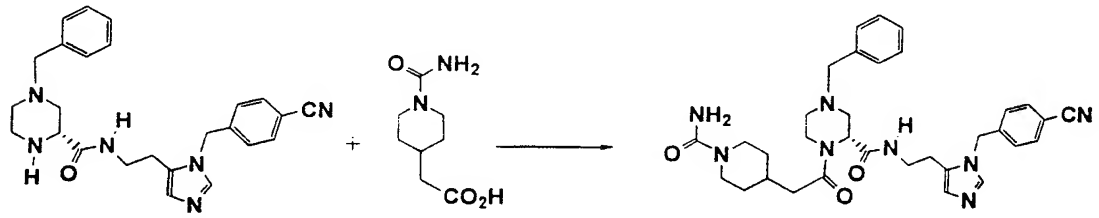
In a similar manner as is described in Preparative Example 12, but using the title compound from Preparative 11 and t-butylisocyanate instead of cyclohexylisocyanate, the title compound is prepared as an off-white solid (66.8 mg, mp = 97.8°C, MH+ = 528).

Example 28P. N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-4-(phenylmethyl)-1-(4-pyridinylacetyl)-2(R)- piperazinecarboxamide N1-oxide



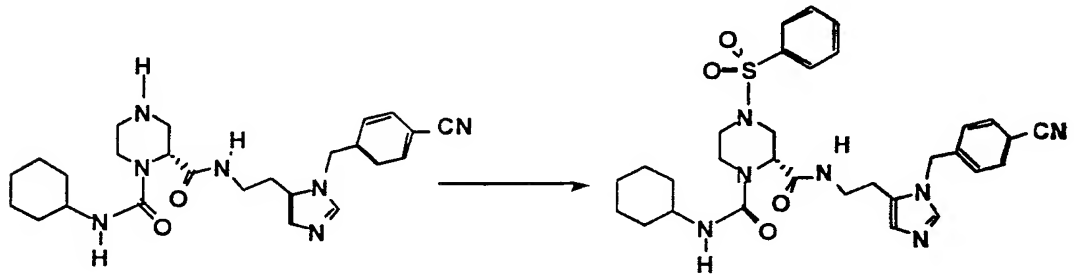
To the title compound from Preparative Example 11 (100 mg, 0.23 mmol) are added HOBt (47 mg, 0.35 mmol), DEC (67 mg, 0.35 mmol), pyridylacetic acid N-oxide (53 mg, 0.35 mmol), NMM (39 mL, 0.35 mmol) and anhydrous DMF (10 mL). The mixture is stirred at room temperature under N_2 overnight. The mixture is concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase is dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by preparative plate chromatography (silica gel) using 6% MeOH-98% CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an off-white solid (54 mg, MH^+ = 564).

Example 28Q. 1-[[1-(aminocarbonyl)-4-piperidinyl]acetyl]-N-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-4-(phenylmethyl)-2(R)-piperazinecarboxamide



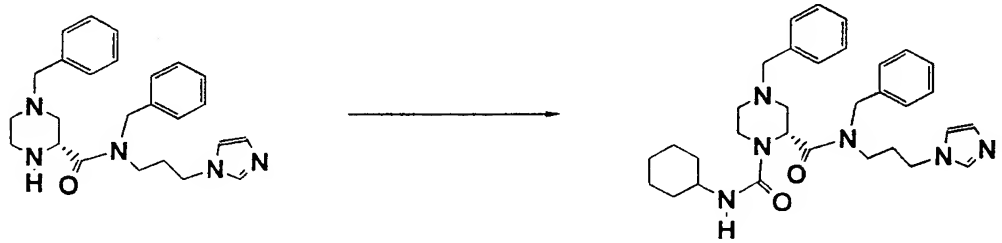
In a similar manner as is described in Example 28P, but using the title compound from Preparative Example 11 and the piperidylacetic acid from Preparative Example instead of pyridylacetic acid N-oxide, the title compound is prepared as an off-white solid (76 mg, 55%, mp = 118.5°C, MH+ = 597).

Example 28R. N2-[2-[1-[(4-Cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-N1-cyclohexyl-4-(phenylsulfonyl)-1,2(R)-piperazinedicarboxamide



To a solution of the title compound from Prepartive Example 8 and 9 (50 mg, 0.12 mmol, 1.0 eq) and triethylamine (0.05 mL, 0.36 mmol) in anhydrous dichloromethane (3 ml) is added benzenesulfonyl chloride (0.02 mL, 0.12 mmol). The resulting mixture is stirred at room temperature under N_2 for 72 hrs, then diluted with additional dichloromethane, washed with aqueous sodium hydroxide (1*M*) and dried over anhydrous MgSO4. The organic phase is filtered, concentrated in vacuo, and the residue purified by preparative plate chromatography (silica gel) using 10% methanol (saturated with ammonia)-90% acetonitrile, and repurified using 5% methanol-dichloromethane saturated with aqueous ammonium hydroxide to afford the title compound as an orange solid (5 mg, mp = 143.6°C, MH+ = 604).

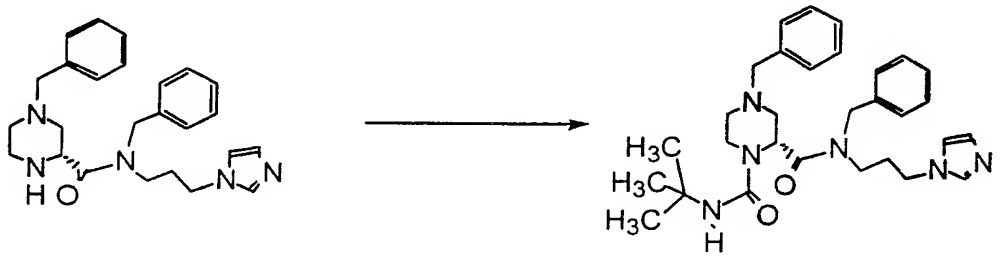
Example 28S. N1-cyclohexyl-N2-[3-(1H-imidazol-1-yl)propyl]-N2,4-bis(phenylmethyl)-1,2(R)- piperazinedicarboxamide



To a solution of the title compound from Example 28Y (0.13 g, 0.3 mmol) dissolved in anhydrous dichloromethane (3 ml) is added cyclohexylisocyanate (0.054 mL, 0.43 mmol) and the resulting solution is stirred at room temperature overnight, then concentrated *in vacuo*. The residue is purified by preparative plate chromatography (silica gel) using

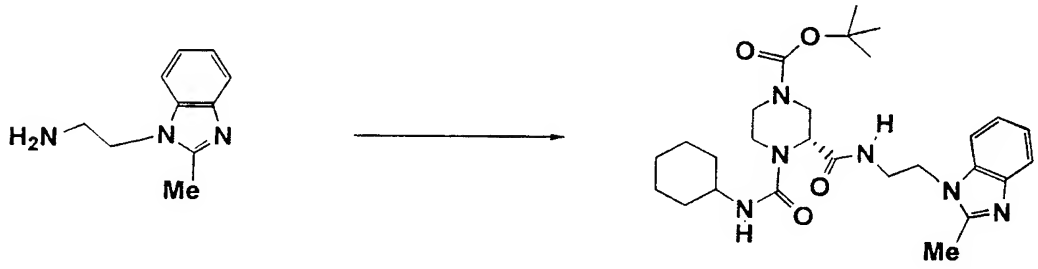
5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a white solid (164 mg, mp = 89.1°C, MH^+ = 543).

Example 28T. N1-(1,1-dimethylethyl)-N2-[3-(1H-imidazol-1-yl)propyl]-N2,4-bis(phenylmethyl)-1,2(R)- piperazinedicarboxamide



To a solution of the title compound from Example 28Y (0.13 g, 0.3 mmol) dissolved in anhydrous dichloromethane (3 ml) is added t-butylisocyanate (0.05 mL, 0.43 mmol) and the resulting solution is stirred at room temperature overnight, then concentrated *in vacuo*. The residue is purified by preparative plate chromatography (silica gel) using 5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a white solid (131 mg, mp = 57.8°C, MH^+ = 517).

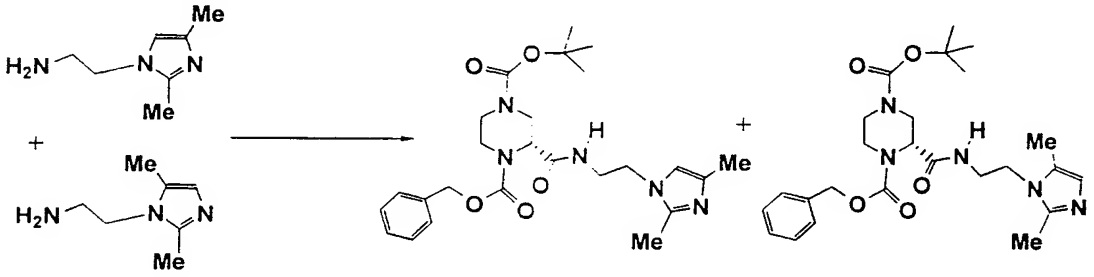
Example 28U. 1,1-dimethyl 1-[(cyclohexylamino)carbonyl]-2(R)-[[[2-(2-methyl-1H-benzimidazol-1-yl)ethyl]amino]carbonyl]-4-piperazinecarboxylate



A solution of the title compound from Preparative Example 14 (0.9 g, 5.14 mmol) and the anhydride from Preparative Example (1.38 g, 1.05 eq) dissolved in anhydrous dichloromethane (10 ml) are stirred at room temperature overnight. Additional anhydride (0.105 g) is added and after 1 hr cyclohexylisocyanate (0.98 mL, 7.71 mmol) is added to the reaction mixture which is stirred for an additional 1.5 hrs. Concentration *in vacuo*

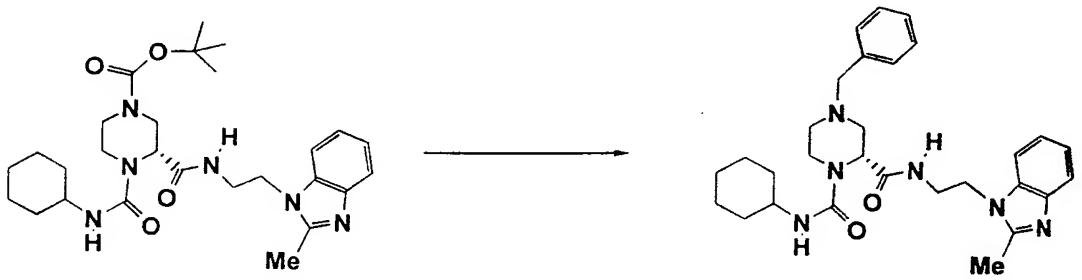
and purification by flash column chromatography (silica gel) using 1-3% MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent affords the title compound as a white solid (1.82 g, mp = 126.9-128.9 °C, MH^+ = 513).

Example 28V. 4-(1,1-dimethylethyl), 1-(phenylmethyl)-2(R)-[[[2-(2,4-dimethyl-1H-imidazol-1-yl)ethyl]amino]carbonyl]-1,4-piperazinedicarboxylate and 4-(1,1-dimethylethyl), 1-(phenylmethyl)-2(R)-[[[2-(2,5-dimethyl-1H-imidazol-1-yl)ethyl]amino]carbonyl]-1,4-piperazinedicarboxylate



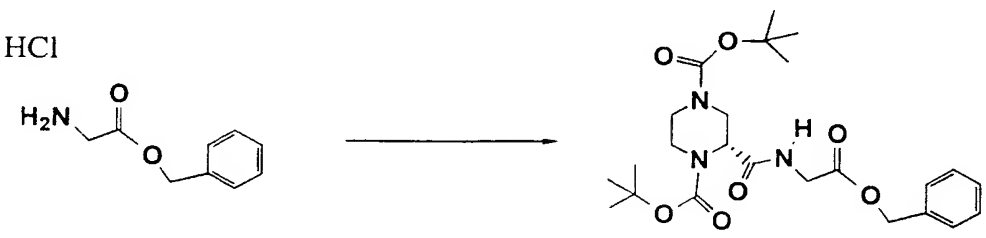
A solution of the title compound from Preparative Example 15 (2.12 g, 15.2 mmol), triethylamine (30.4 mmol) and the anhydride from Preparative Example (3.89 g, 15.2 mmol) dissolved in anhydrous dichloromethane (30 ml) is stirred at room for 30 min. Benzyloxycarbonylsuccinamide (4.17 g, 16.7 mmol) is added and the resulting mixture is stirred at room temperature overnight. Concentration *in vacuo* and purification by flash column chromatography (silica gel) using 2% MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent affords the title compound as a (2.57 g). The regioisomers are separated by HPLC (Chiracel AD column) using 5% isopropanol-95% hexane-0.2% diethylamine to give the 2,4-dimethyl isomer (mp = 64.2 °C, MH^+ = 486) and the 2,5-dimethyl isomer (mp = 71.5 °C, MH^+ = 486).

Example 28W. N1-cyclohexyl-N2-[2-(2-methyl-1H-benzimidazol-1-yl)ethyl]-4-(phenylmethyl)-1,2(R)- piperazinedicarboxylate



A solution of the title compound from Example 28U (101) (0.49 g, 0.89 mmol) dissolved in anhydrous dichloromethane (10 ml) and trifluoroacetic acid (2 ml) are stirred at room temperature for 3 hrs. The resulting solution is concentrated *in vacuo*, then the residue is combined with anhydrous dichloromethane (10 ml), benzaldehyde (0.28 mL, 2.68 mmol), glacial acetic acid (1 mL) and sodium triacetoxyborohydride (0.76 g, 3.6 mmol) and stirred at room temperature for 48 h. The reaction mixture is concentrated *in vacuo*, diluted with dichloromethane and washed with 1*N* NaOH (aq). The organic phase is dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (silica gel) using 1-3% MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent to afford the title compound as a white solid (0.40 g, mp = 192.9-194.9 °C, MH^+ = 503).

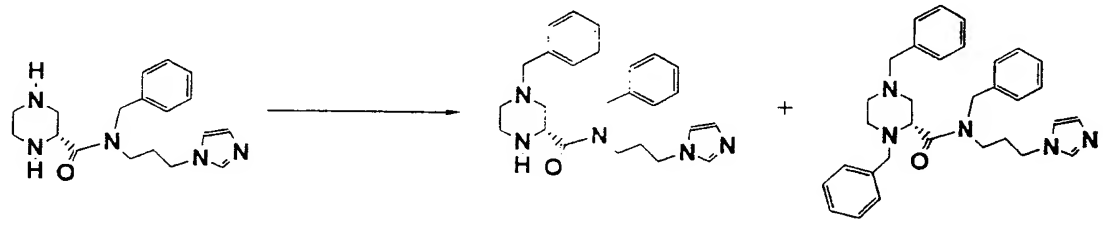
Example 28X. Bis(1,1-dimethylethyl) 2(R)-[[[2-(phenylmethoxy)ethyl]amino]carbonyl]-1,4- piperazinedicarboxylate



A solution of benzyl 2-aminoacetate hydrochloride (1.3 g, 7.8 mmol), triethylamine (3.26 mL, 23.4 mmol) and the anhydride from Preparative Example (2 g, 7.8 mmol) dissolved in anhydrous

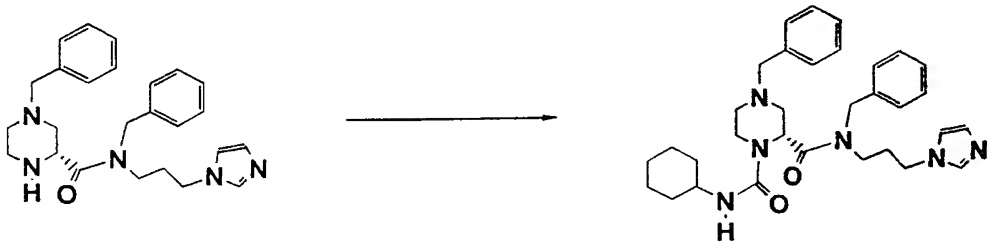
dichloromethane (40 ml) are stirred at room temperature overnight. The reaction mixture is diluted with dichloromethane and washed with 1*N* NaOH (aq) and brine. The organic phase is dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a white solid (1.03 g, MH^+ = 478 (35%), 322(100%)).

Example 28Y. N2-[3-(1H-imidazol-1-yl)propyl]N2,4-bis(phenylmethyl)-1,2(R)-piperazinecarboxamide and N2-[3-(1H-imidazol-1-yl)propyl]N1,2,4-tris(phenylmethyl)-1,2(R)-piperazinecarboxamide



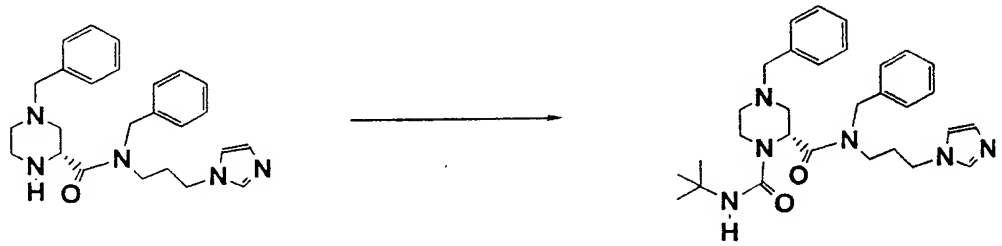
To the title compound from Preparative Example 17 (381 mg, 1.16 mmol) and benzaldehyde (0.12 mL, 1.16 mmol) dissolved in glacial acetic acid (1 mL) and anhydrous dichloromethane (15 ml) at 0°C are added sodium triacetoxyborohydride (740 mg, 3.5 mmol) and the resulting mixture is warmed to room temperature and stirred for an additional 12 h. The reaction mixture is washed with 1*N* NaOH (aq) and the organic phase is dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by preparative plate chromatography (silica gel) using 2-5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title dibenzyl compound (256 mg, MH^+ = 418) and the title tribenzyl compound (78.4 mg, MH^+ = 508).

Example 28Y1. N1-CYCLOHEXYL-N2-[3-(1H-IMIDAZOL-1-YL)PROPYL]-N2,4-BIS(PHENYLMETHYL)-1,2(R)-PIPERAZINEDICARBOXAMIDE



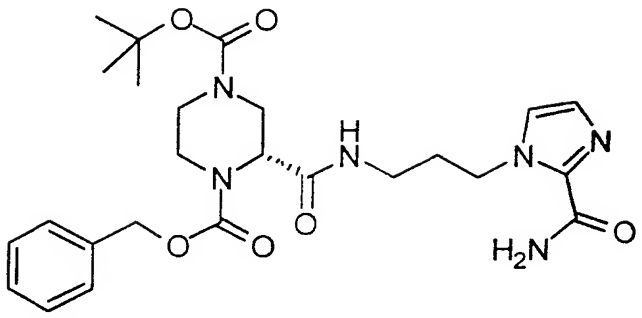
To a solution of the title compound from Example 28Y (0.13 g, 0.3 mmol) dissolved in anhydrous dichloromethane (3 ml) was added cyclohexylisocyanate (0.054 mL, 0.43 mmol) and the resulting solution was stirred at room temperature overnight, then concentrated in vacuo. The residue was purified by preparative plate chromatography (silica gel) using 5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a white solid (164 mg, 99%, mp = 89.1°C, MH^+ = 543).

Example 28Y2. N1-(1,1-DIMETHYLETHYL)-N2-[3-(1H-IMIDAZOL-1-YL)PROPYL]-N2,4-BIS(PHENYLMETHYL)-1,2(R)-PIPERAZINE-DICARBOXAMIDE



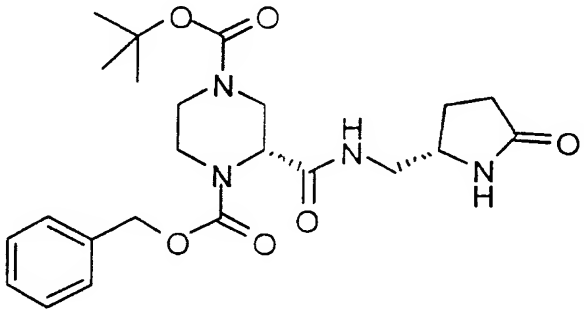
To a solution of the title compound from Example 28Y (0.13 g, 0.3 mmol) dissolved in anhydrous dichloromethane (3 ml) was added t-butylisocyanate (0.05 mL, 0.43 mmol) and the resulting solution was stirred at room temperature overnight, then concentrated in vacuo. The residue was purified by preparative plate chromatography (silica gel) using 5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a white solid (131 mg, 83%, mp = 57.8°C, MH^+ = 517).

Example 28Z.



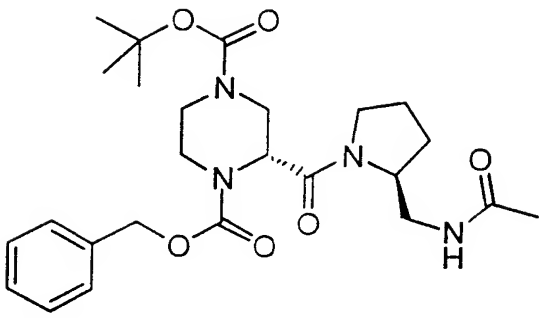
A solution of the title compound from Step B of Preparative Example 23 (0.23 g, 0.86 mmol) is stirred in 4M HCl in dioxane (4 mL) at room temperature overnight. The solution is concentrated and stirred with CH_2Cl_2 (10 mL), DMF (10 mL) and TEA (0.47 mL, 5 eq.) before adding piperazine anhydride (0.26g, 1.2 eq.) portionwise. The resulting solution is stirred at room temperature 1.5 hours and additional anhydride added (0.043g, 0.2 eq.). The reaction mixture is stirred 0.5 hours before adding CBZ-OSuc (0.28g, 1.2 eq.). The resulting solution is stirred 3 hours and quenched by the addition of $NaHCO_3$ (10 mL), diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 X 50 mL). The combined organics are dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product is purified by flash chromatography using a 5% MeOH in CH_2Cl_2 solution as eluent to give a white solid (0.32 g): mp= 71-75 °C; LCMS: MH^+= 515.

Example 28 Z1



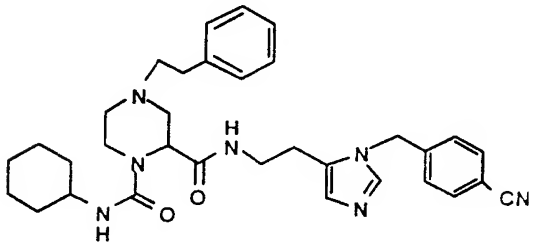
By essentially the same procedure as set forth in Example 28 Z, except using the title compound from Step B of Preparative Example 24, the title compound is prepared (1.66 g): mp= 77-79 °C; LCMS: MH^+= 461.

Example 28 Z2.



By essentially the same procedure set forth in Example 28 Z except using the title compound from Step C of Preparative Example 25 (0.17g, 0.950 mmol), the title compound is prepared (0.37 g): mp= 58-60 °C; LCMS: MH^+= 489.

Example 29. **PS 287238-1-0**

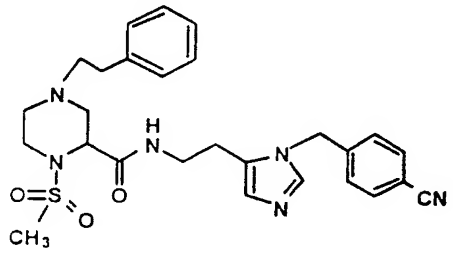


Accurate Mass ([M+H]$^+$)

Calculated: 568

Found: 568

Example 30. **PS 812520-1-0**

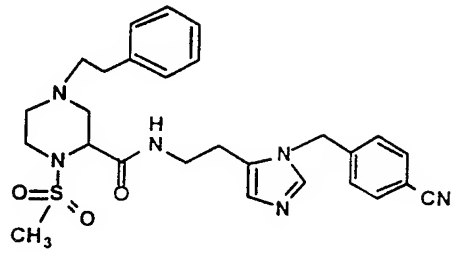


Accurate Mass ([M+H]$^+$)

Calculated: 521

Found: 521

Example 31. **PS 465781-1-0**

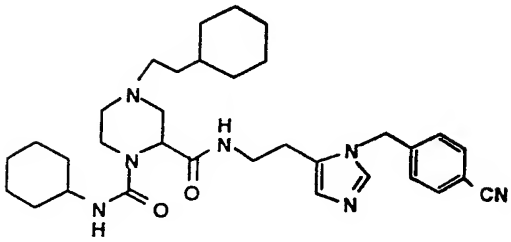


Accurate Mass ([M+H]$^+$)

Calculated: 527

Found: 527

Example 32. **PS 461400-1-0**

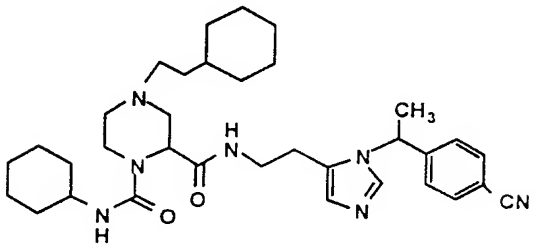


Accurate Mass ([M+H]$^+$)

Calculated: 574

Found: 574

Example 33. **PS 815156--1-0**

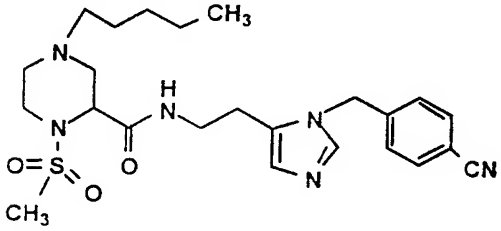


Accurate Mass ([M+H]$^+$)

Calculated: 588

Found: 588

Example 34. **PS 159773-1-0**

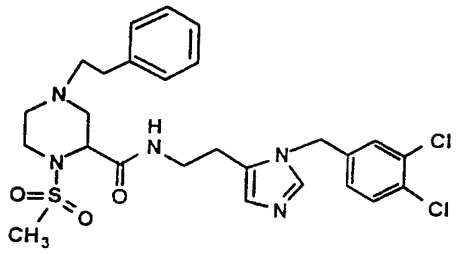


Accurate Mass ([M+H]$^+$)

Calculated: 487

Found: 487

Example 35. **PS 372802-1-0**

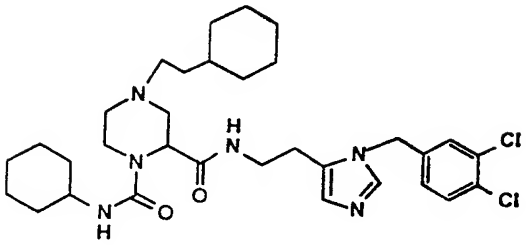


Accurate Mass ([M+H]$^+$)

Calculated: 564

Found: 564

Example 36. **PS 793961-1-0**

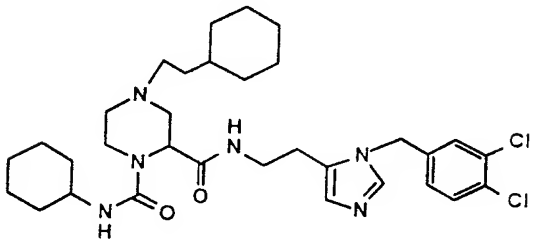


Accurate Mass ([M+H]$^+$)

Calculated: 617

Found: 617

Example 37. **PS 321542-1-0**

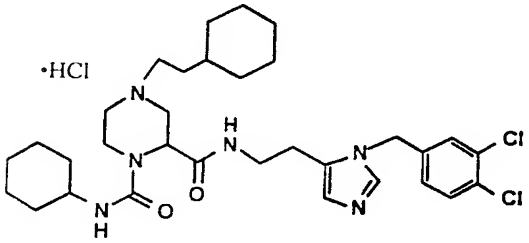


Accurate Mass ([M+H]$^+$)

Calculated: 617

Found: 617

Example 38. **PS 288326-1-0**

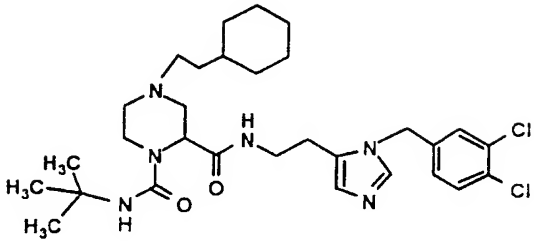


Accurate Mass ([M+H]$^+$)

Calculated: 617

Found: 617

Example 39. **PS 478500-1-0**

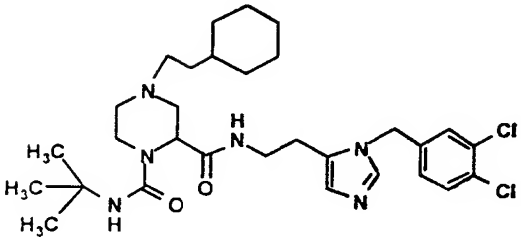


Accurate Mass ([M+H]$^+$)

Calculated: 592

Found: 592

Example 40. **PS 783003-1-0**

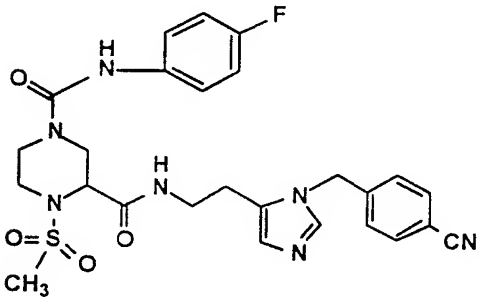


Accurate Mass ([M+H]$^+$)

Calculated: 591

Found: 591

Example 41. **PS 241936-1-0**

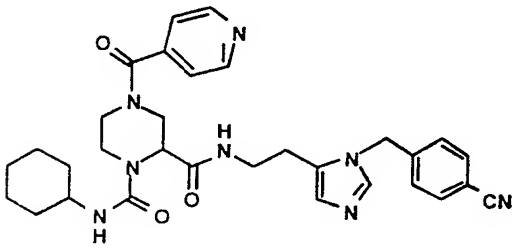


Accurate Mass ([M+H]$^+$)

Calculated: 554

Found: 554

Example 42. **PS 409643-1-0**

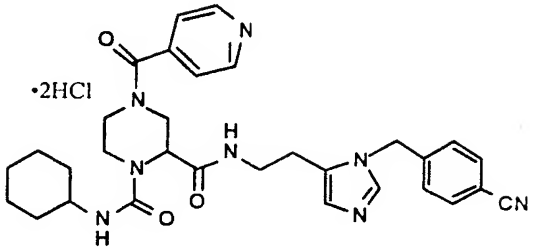


Accurate Mass ([M+H]$^+$)

Calculated: 569

Found: 569

Example 43. **PS 725556-1-0**

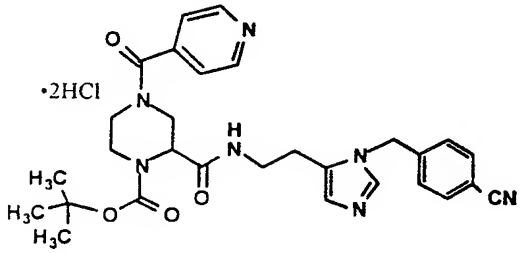


Accurate Mass ([M+H]$^+$)

Calculated: 569

Found: 569

Example 44. **PS 769295-1-0**

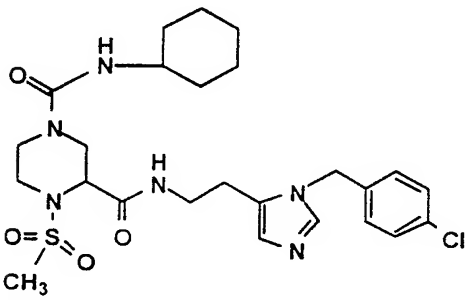


Accurate Mass ([M+H]$^+$)

Calculated: 544

Found: 544

Example 45. **PS 075114-1-0**

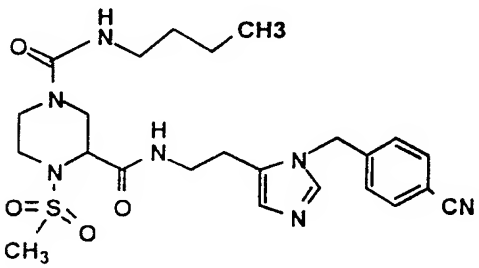


Accurate Mass ([M+H]$^+$)

Calculated: 551

Found: 551

Example 46. **PS 990951-1-0**

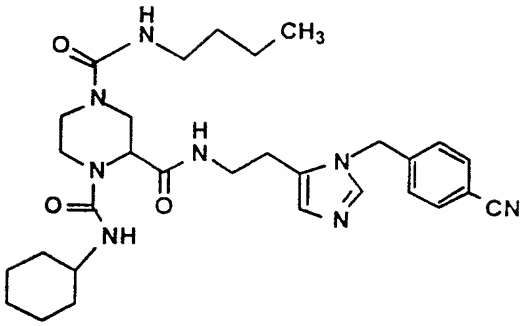


Accurate Mass ([M+H]$^+$)

Calculated: 516

Found: 516

Example 47. **PS 192638-1-0**

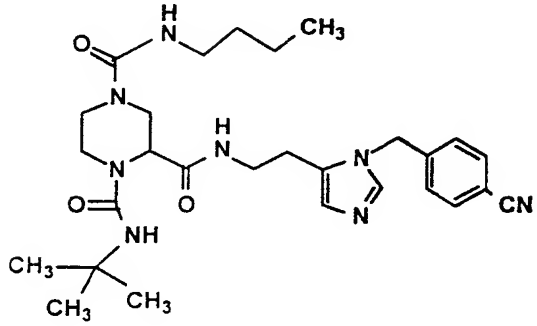


Accurate Mass ([M+H]$^+$)

Calculated: 563

Found: 563

Example 48. **PS 354164-1-0**

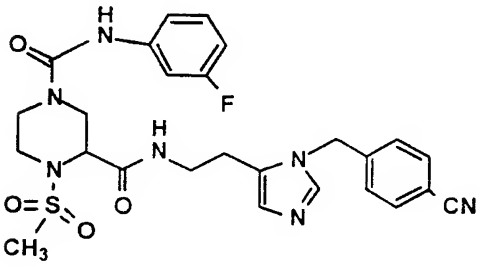


Accurate Mass ([M+H]$^+$)

Calculated: 537

Found: 537

Example 49. **PS 395570-1-0**

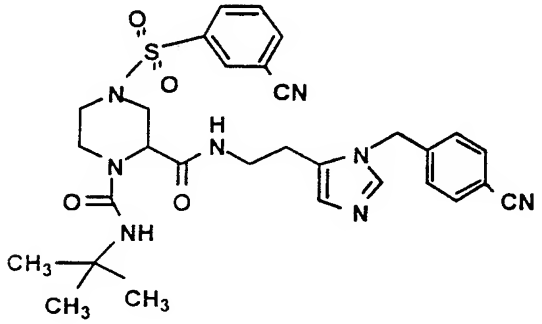


Accurate Mass ([M+H]$^+$)

Calculated: 554

Found: 554

Example 50. **PS 956973-1-0**

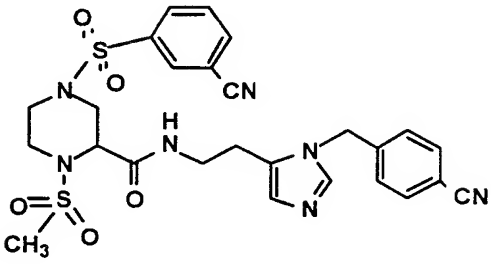


Accurate Mass ([M+H]$^+$)

Calculated: 603

Found: 603

Example 51. **PS 859989-1-0**

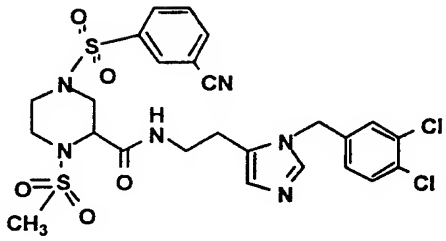


Accurate Mass ([M+H]$^+$)

Calculated: 582

Found: 582

Example 52. **PS 467023-1-0**

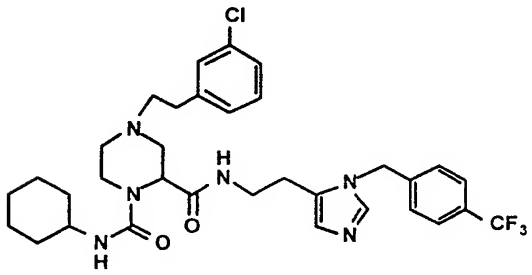


Accurate Mass ([M+H]$^+$)

Calculated: 625

Found: 625

Example 53. **PS 437810-1-0**

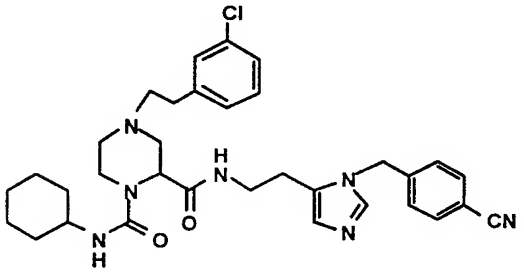


Accurate Mass ([M+H]$^+$)

Calculated: 645

Found: 645

Example 54. **PS 381385-1-0**

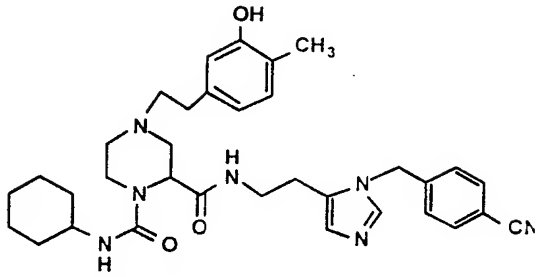


Accurate Mass ([M+H]$^+$)

Calculated: 602

Found: 602

Example 55. **PS 201633-1-0**

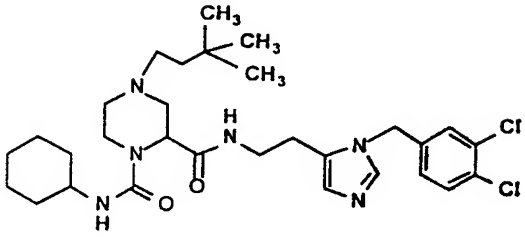


Accurate Mass ([M+H]$^+$)

Calculated: 596

Found: 596

Example 56. **PS 593455-1-0**

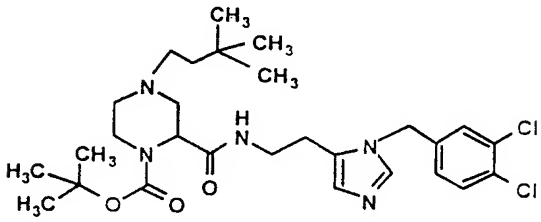


Accurate Mass ([M+H]$^+$)

Calculated: 591

Found: 591

Example 57. **PS 320451-1-0**

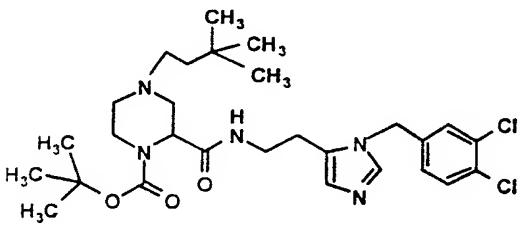


Accurate Mass ([M+H]$^+$)

Calculated: 566.

Found: 566.

Example 57A. **PS 477090-1-0**

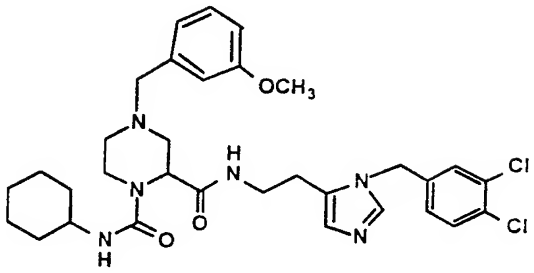


Accurate Mass ([M+H]$^+$)

Calculated: 565.

Found: 565

Example 58. **PS 130057-1-0**

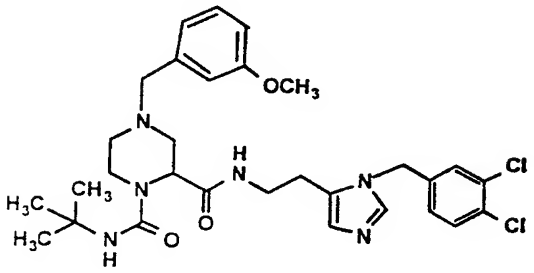


Accurate Mass ([M+H]$^+$)

Calculated: 628

Found: 628

Example 59. **PS 516972-1-0**

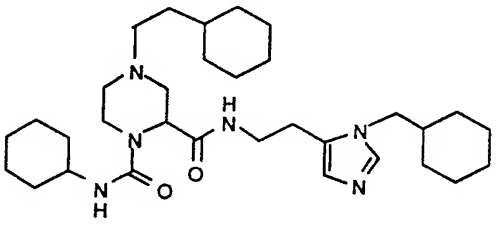


Accurate Mass ([M+H]$^+$)

Calculated: 601

Found: 601

Example 60. **PS 064691-1-0**

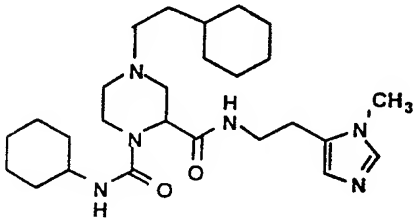


Accurate Mass ([M+H]$^+$)

Calculated: 556

Found: 556

Example 61. **PS 028348-1-0**

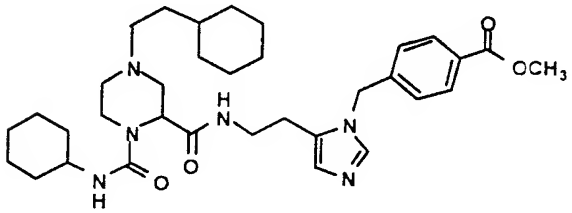


Accurate Mass ([M+H]$^+$)

Calculated: 556

Found: 556

Example 62. **PS 410892-1-0**

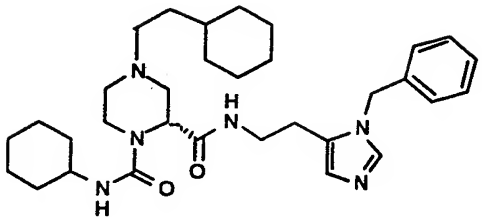


Accurate Mass ([M+H]$^+$)

Calculated: 607

Found: 607

Example 64. **PS 813558-1-0**

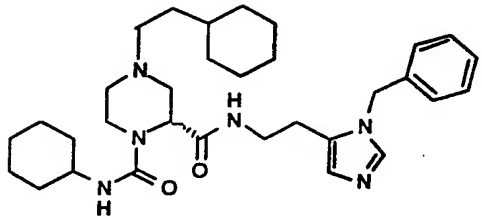


Accurate Mass ([M+H]$^+$)

Calculated: 549

Found: 549

Example 65. **PS 319448-1-0**

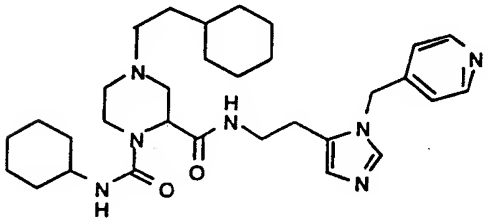


Accurate Mass ([M+H]$^+$)

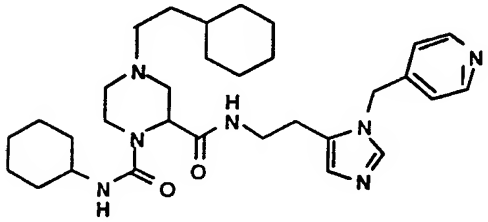
Calculated: 549

Found: 549

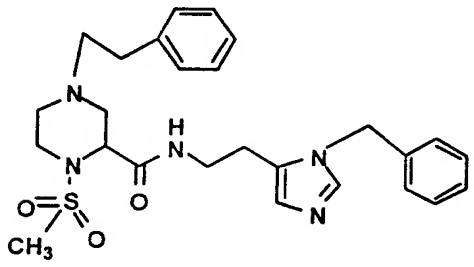
Example 66. **PS 4200838-1-0**



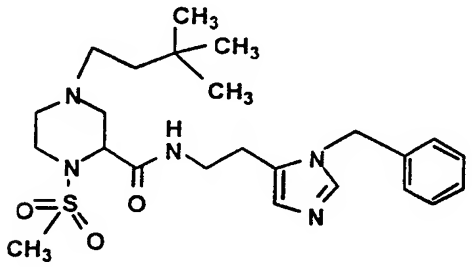
Example 67. **PS 259236-1-0**



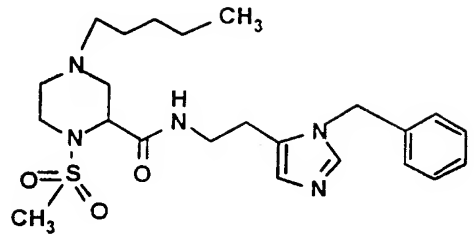
Example 68.



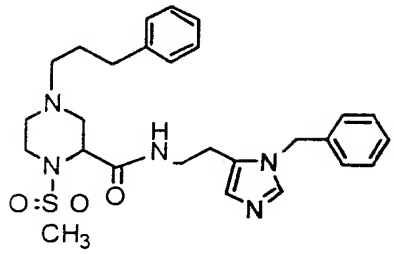
Example 69.



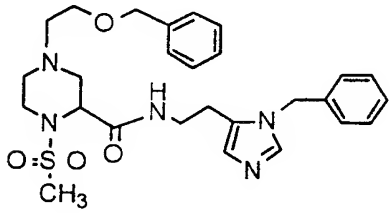
Example 70.



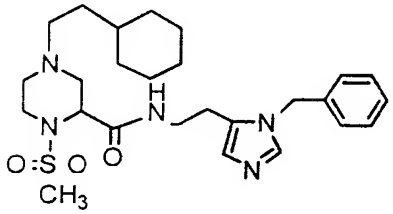
Example 71



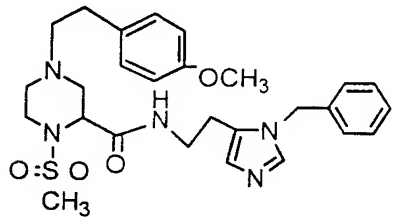
Example 72



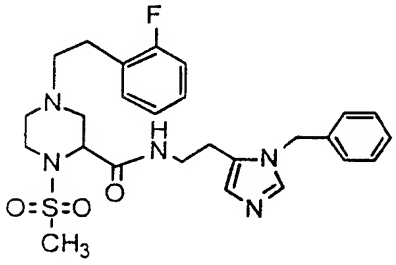
Example 73.



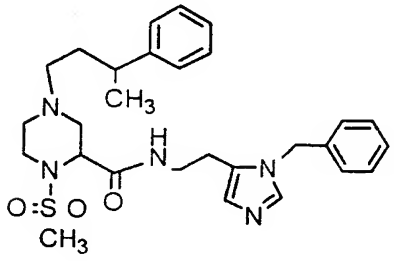
Example 74



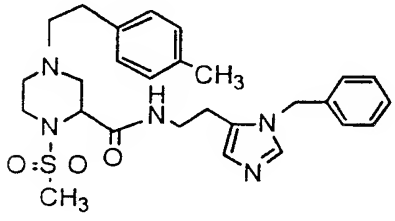
Example 75



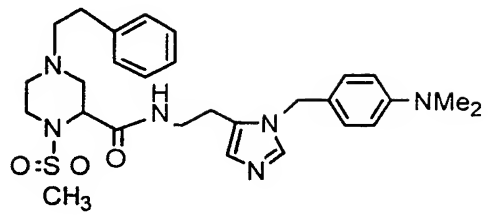
Example 76



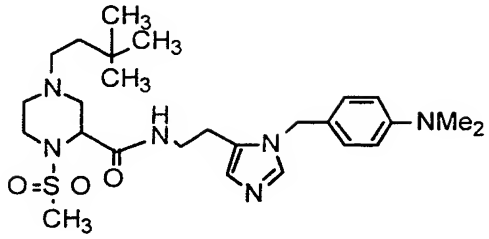
Example 77



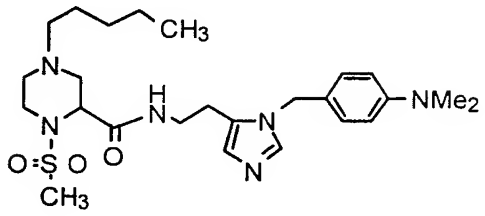
Example 78



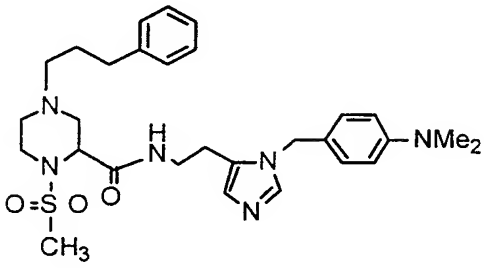
Example 79



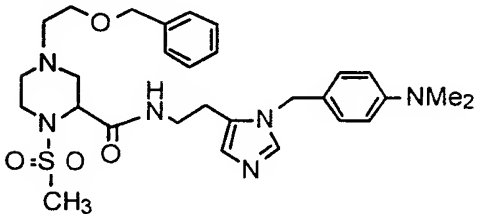
Example 80



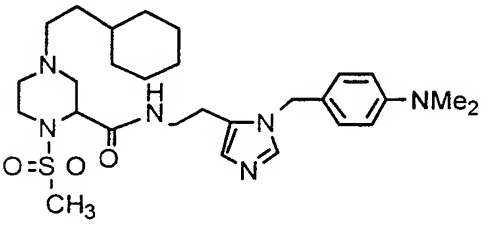
Example 81



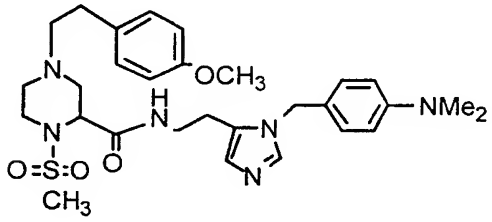
Example 82



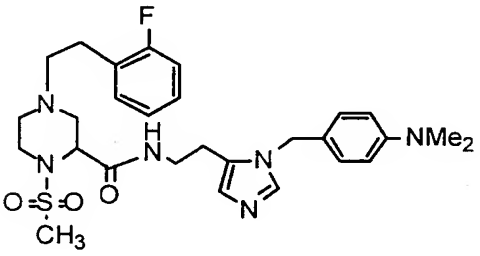
Example 83



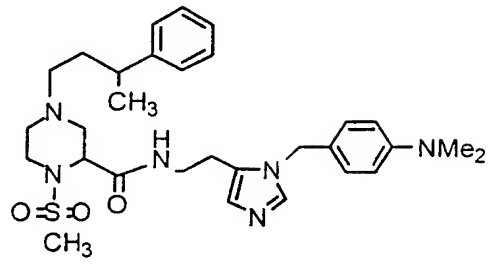
Example 84



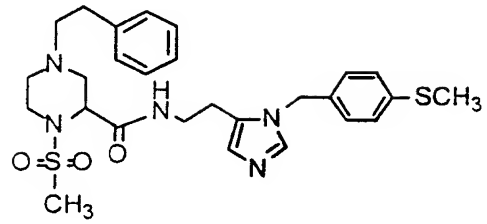
Example 85



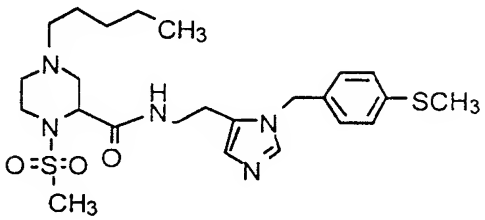
Example 86



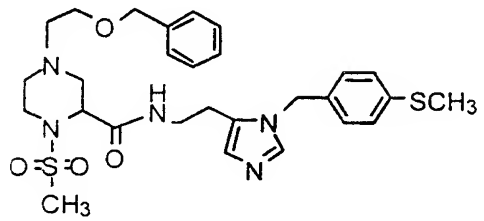
Example 87



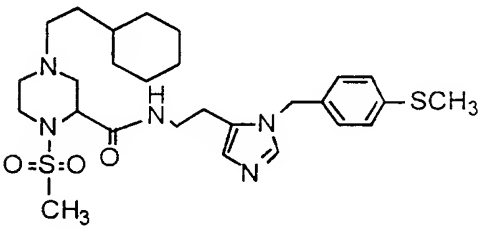
Example 88



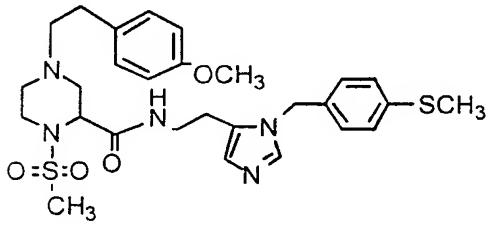
Example 89



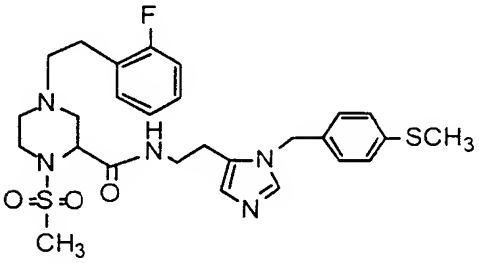
Example 90



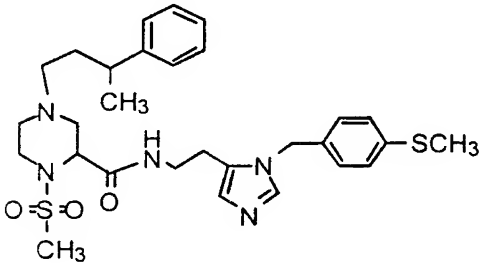
Example 91



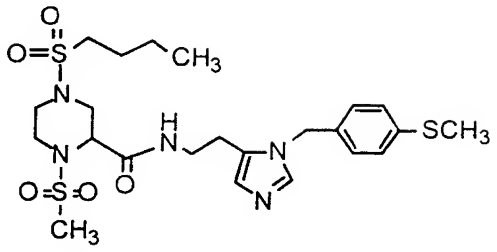
Example 92



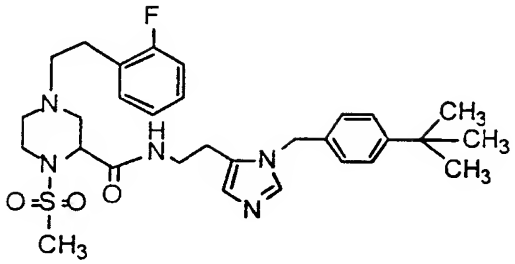
Example 93



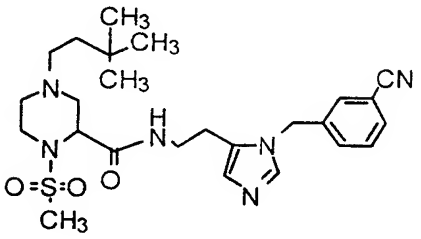
Example 94



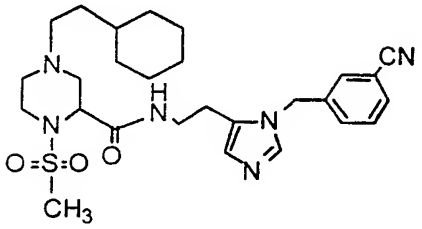
Example 95



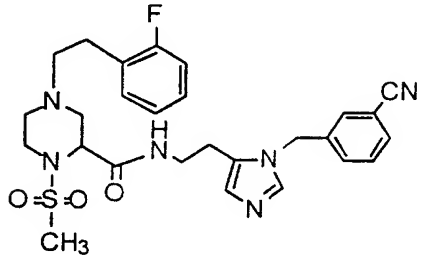
Example 96



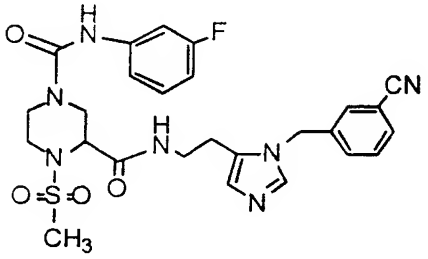
Example 97



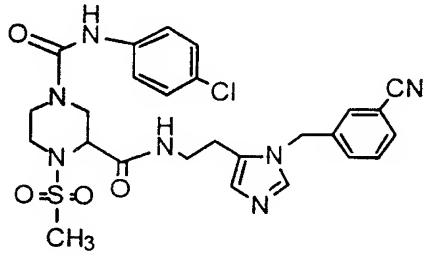
Example 98



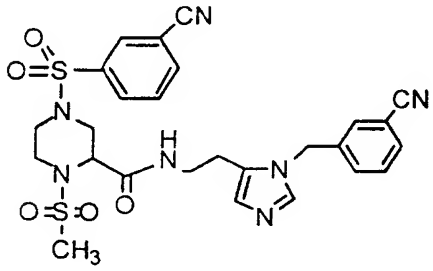
Example 99



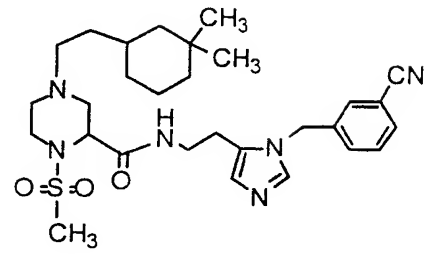
Example 100



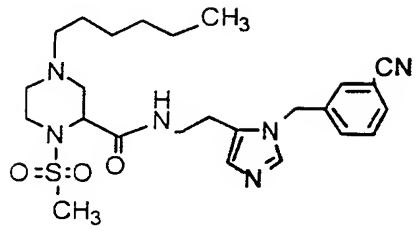
Example 101



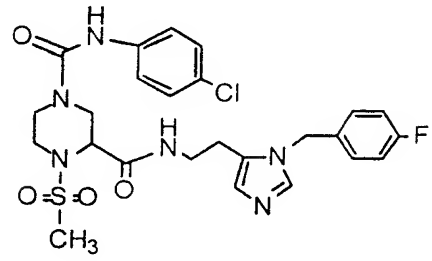
Example 102



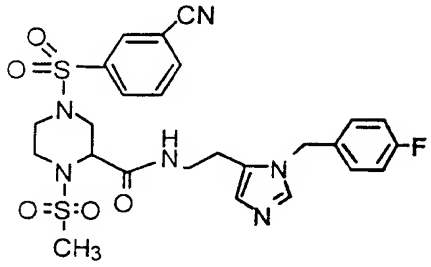
Example 103



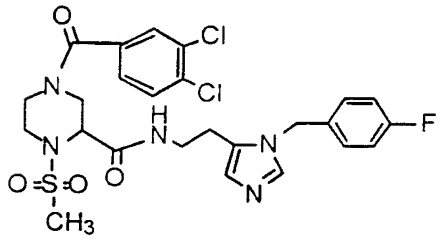
Example 104



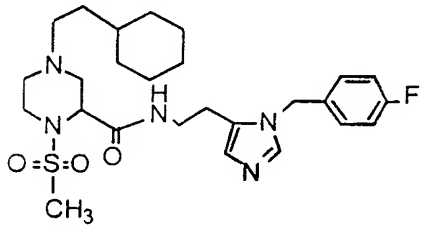
Example 105



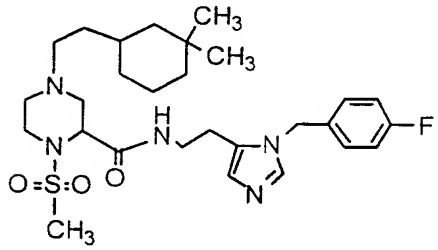
Example 106



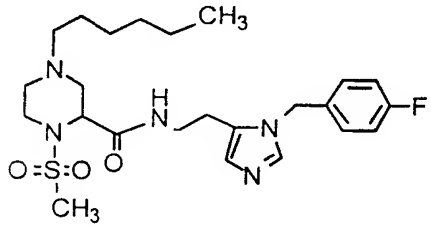
Example 107



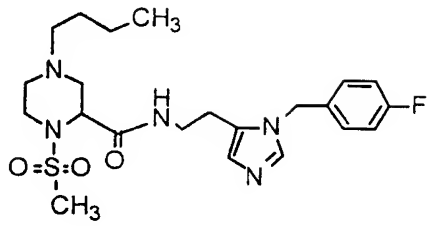
Example 108



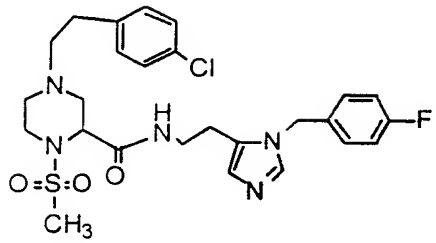
Example 109



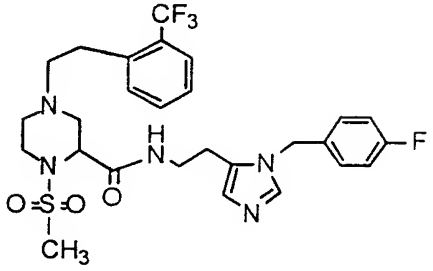
Example 110



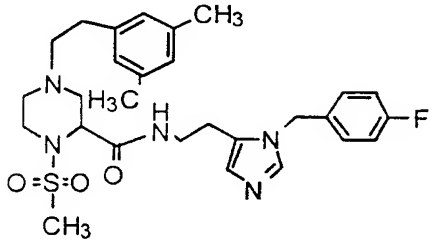
Example 111



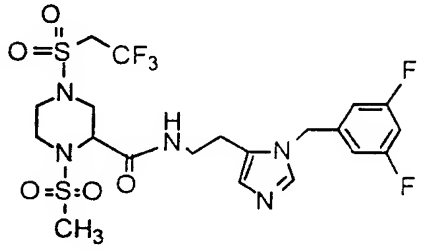
Example 112



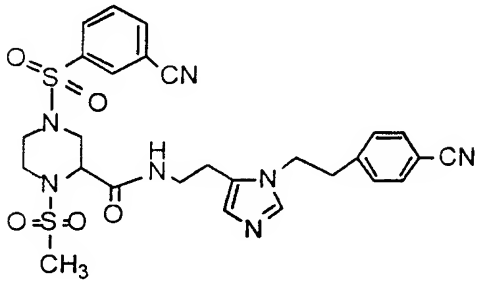
Example 113



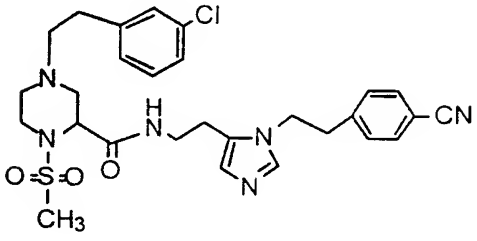
Example 114



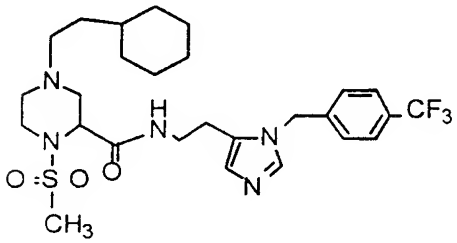
Example 115



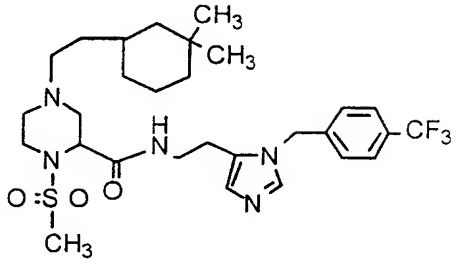
Example 116



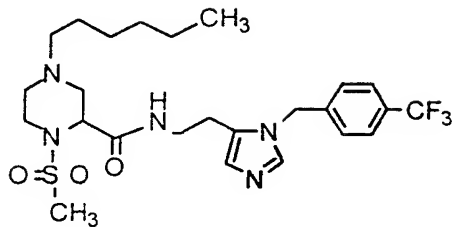
Example 117



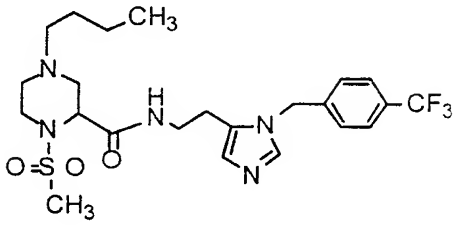
Example 118



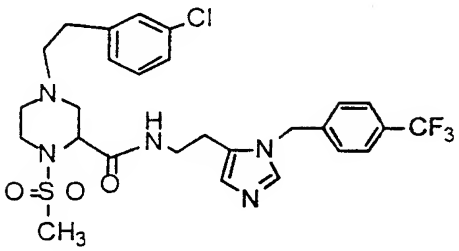
Example 119



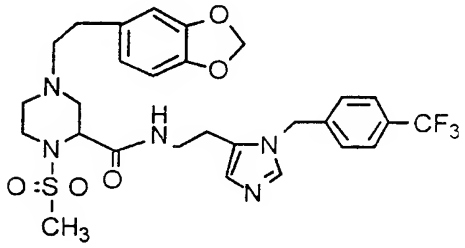
Example 120



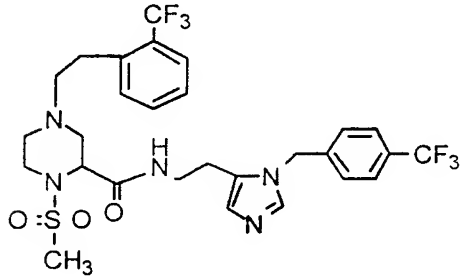
Example 121



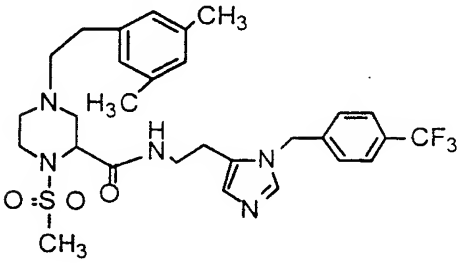
Example 122



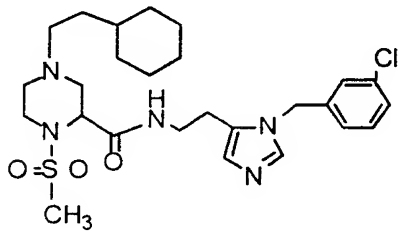
Example 123



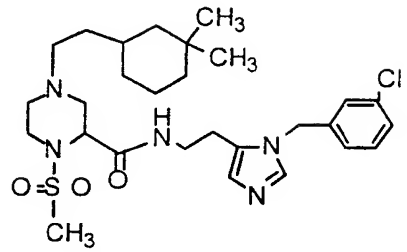
Example 124



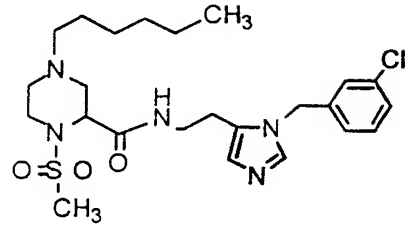
Example 125



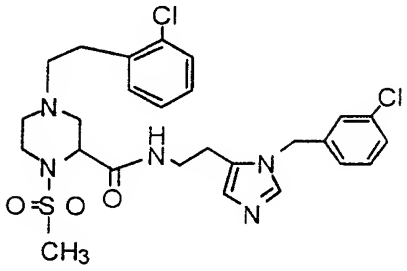
Example 126



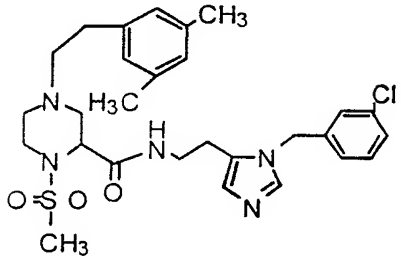
Example 127



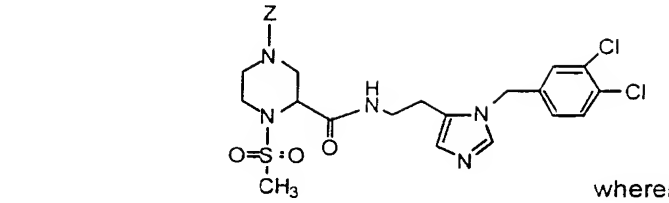
Example 128



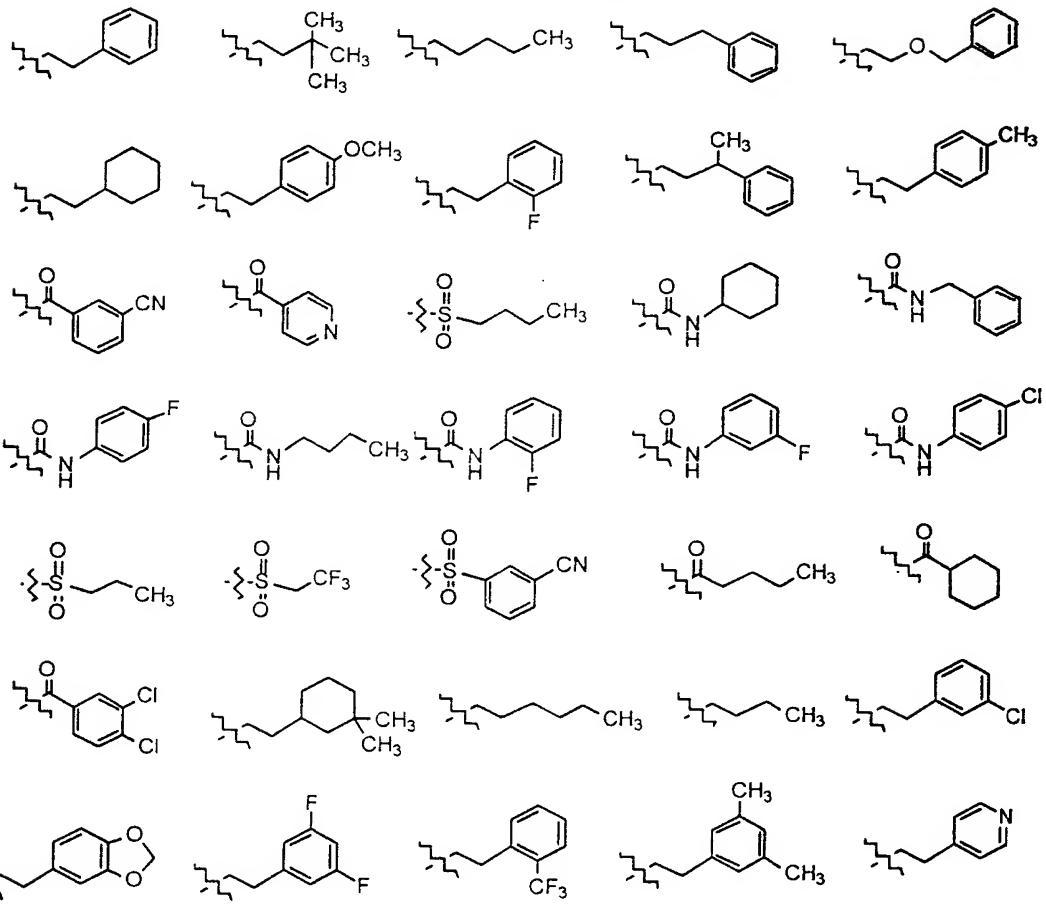
Example 129



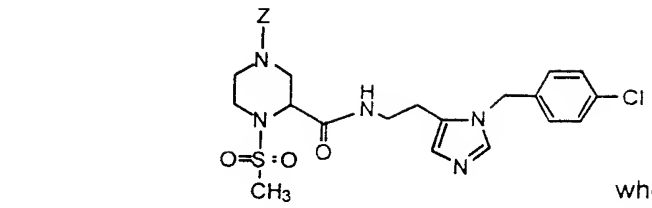
Examples 130-165.



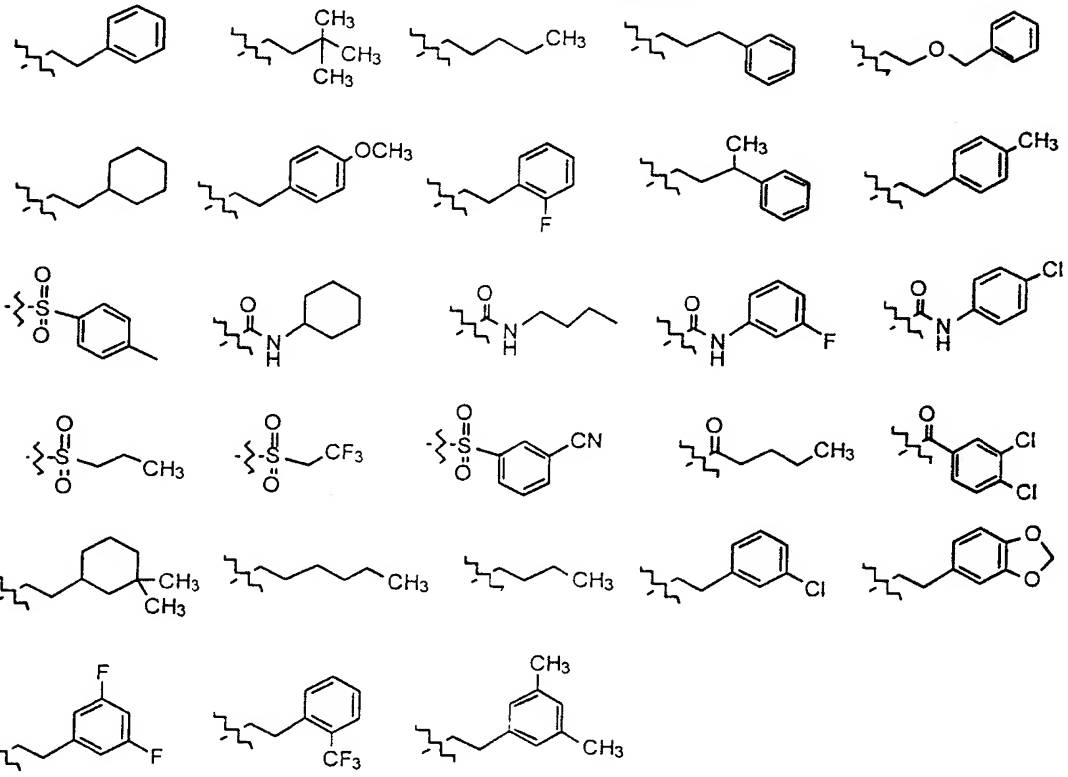
wherein Z =



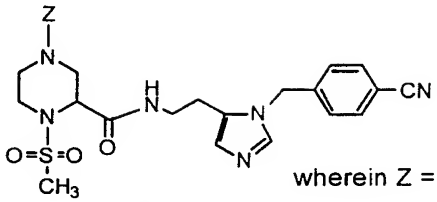
Examples 165-193:



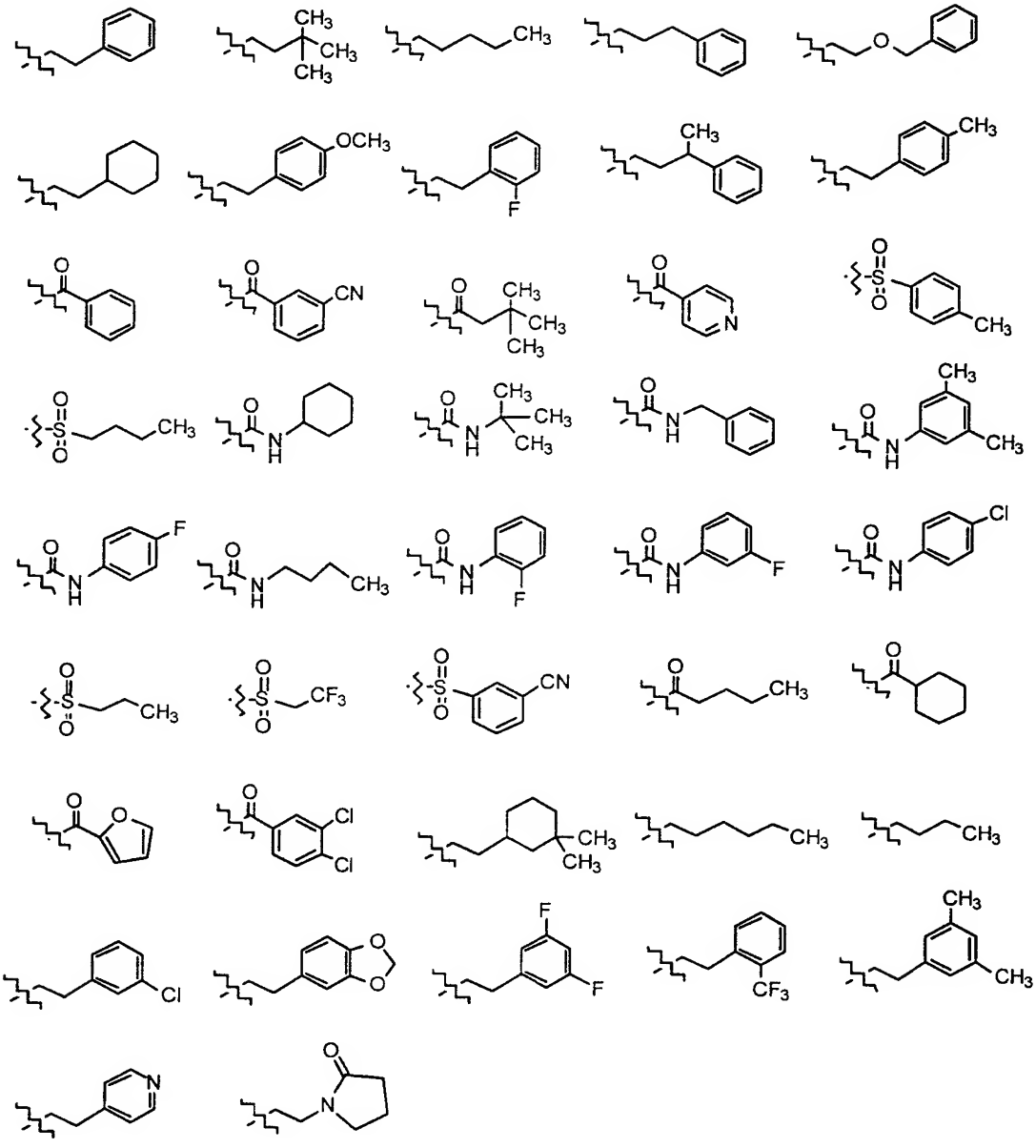
wherein Z =



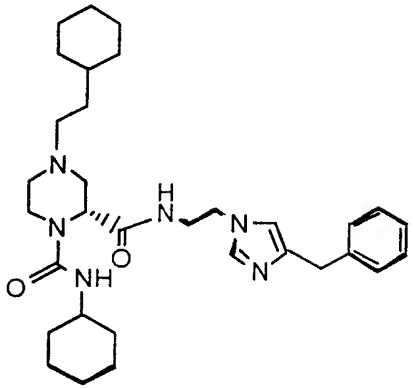
Examples 193-235:



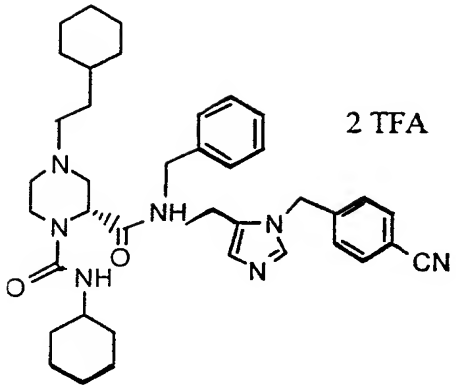
wherein Z =



Examples 236-237



PS204446

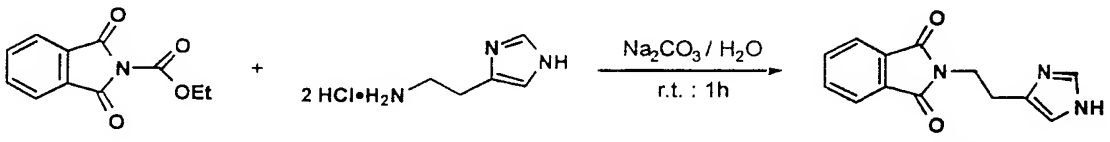


PS365776

PREPARATION OF STARTING MATERIALS

Starting materials useful in preparing the compounds of the present invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Methods for preparing various starting materials can also be found in references such as, for example, Emmett, J. C., Holloway, F. H., Turner, J. L. J. Chem. Soc., Perkin Trans. 1 1979, 1341-1344 and Abdel-Magid, A. F., Maryanoff, C. A., Carson, K. G. *Tetrahedron Lett.* 1990, *31*, 5595.

Preparative Example 1.

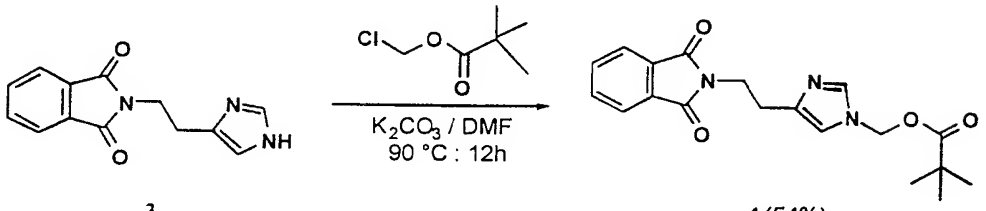


1 2 3 (98%)

N-Carbethoxyphthalimide **1** (62.8 g, 0.275 mol, 1.1 eq.) is added portionwise over a period of 30 minutes to a stirred solution of histamine dihydrochloride **2** (46.7 g, 0.250 mol, 1.0 eq.) and sodium carbonate (54.3 g, 0.513 mol, 2.05 eq.) in distilled water (1250 ml) at room temperature. The resulting snow-white suspension is stirred vigorously at room temperature for 90 minutes. The solid is filtered off and thoroughly washed with ice-cold distilled water (4 x 50 ml). The solid is collected and dried under vacuum over P_2O_5 at 60 °C for 12h to give N^a-phthaloylhistamine **3**

(59.2 g, 0.245 mol, 98%) in high purity (>95% by ^{1}H NMR). The snow-white solid is used directly without further purification.

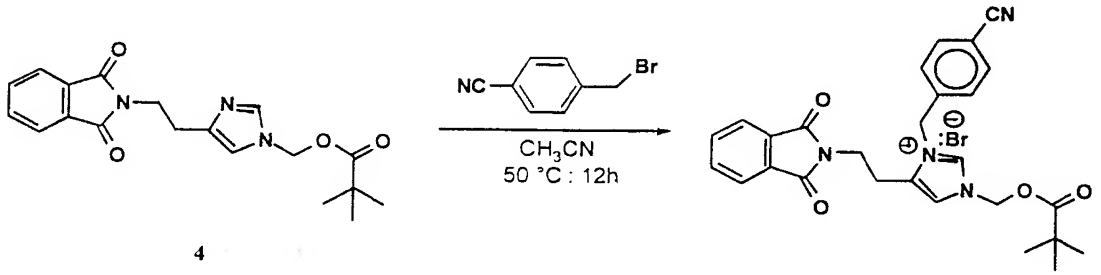
Preparative Example 2.



3 4 (54%)

A solution of chloromethyl pivalate (18.5 ml, 0.125 mol, 1.2 eq.) in anhydrous *N,N*-dimethylformamide (DMF, 100 ml) is added dropwise over a period of one hour to a stirred mixture of **3** (25.0 g, 0.104 mol, 1.0 eq.) and potassium carbonate (17.2 g, 0.125 mol, 1.2 eq.) in anhydrous DMF (500 ml) at 90 °C under a nitrogen atmosphere. The mixture is stirred at 90 °C for 12h. The volatiles are removed under vacuum at 50 °C. The residue is taken up in brine (100 ml) and extracted with ethyl acetate (4 x 25 ml). The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated under vacuum at 30 °C. The residual off-white solid is flash-chromatographed (hexanes : acetone = 6 : 4 v/v) over silica gel to give *N^t-pivaloyloxymethyl-N^a-phthaloylhistamine* **4** (20 g, 0.056 mol) as a crystalline, white solid of high purity.

Preparative Example 3.

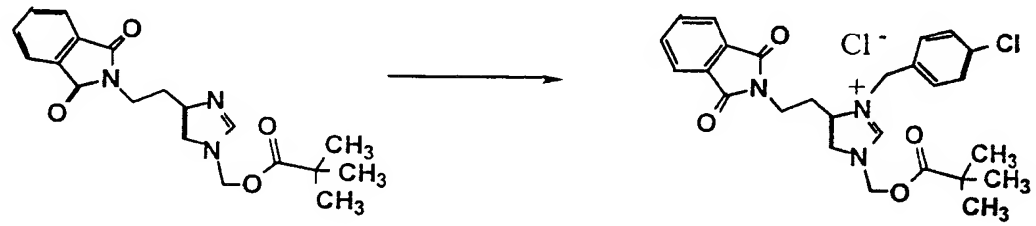


4 5 (91%)

A solution of **4** (10.2 g, 28.7 mmol, 1.0 eq.) and *a*-bromo-*p*-tolunitrile (11.4 g, 57.4 mmol, 2.0 eq.) is stirred in anhydrous acetonitrile (150 ml) at 50 °C under a nitrogen atmosphere for 12h. The resulting snow-white suspension is cooled to room temperature and chilled in a refrigerator at -

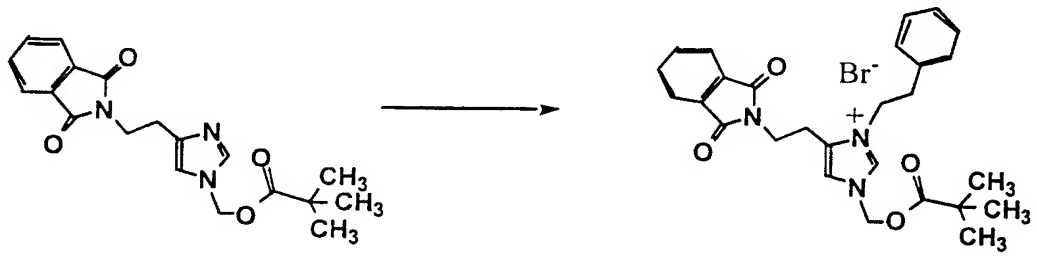
20 °C for one hour. The precipitate is filtered off and thoroughly washed with ice-cold ethyl acetate (4 x 50 ml). The solid is collected and dried under vacuum over P_2O_5 at 50 °C for 12h to give *1-pivaloyloxymethyl-3-(4-cyanobenzyl)-4-(2-phthalimidoethyl)imidazolium bromide* **5** (14.4 g, 26.2 mmol).

Preparative Example 3A. 1-Pivaloyloxymethyl-3-(4-chlorobenzyl)-4-(2-phthalimidoethyl)imidazolium chloride



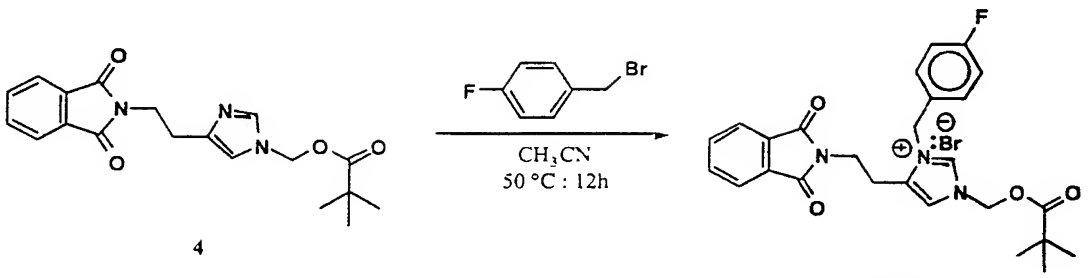
A solution of the title compound from Preparative Example 2 (5 g, 14.1 mmol) and 4-chlorobenzylchloride (2.5 g, 15.5 mmol) was stirred in anhydrous acetonitrile (60 ml) at reflux under a nitrogen atmosphere for 48 h. The mixture was concentrated in vacuo and recrystallized from ethyl acetate-hexane to give the title compound as a solid (3.2 g, MH+ = 480), and the filtrate which was concentrated to give additional product (3.6 g).

Preparative Example 3B. 1-Pivaloyloxymethyl-3-(4-phenylethyl)-4-(2-phthalimidoethyl)imidazolium bromide



A solution of the title compound from Preparative Example 2 (5 g, 14.1 mmol) and 2-bromoethylbenzene (15.5 mmol, 1.1 eq) is stirred in anhydrous acetonitrile (50 ml) at reflux under a nitrogen atmosphere for 72 h. The mixture is concentrated in vacuo to give the title compound as a sticky oil (100%, MH+ = 460).

Preparative Example 3C.

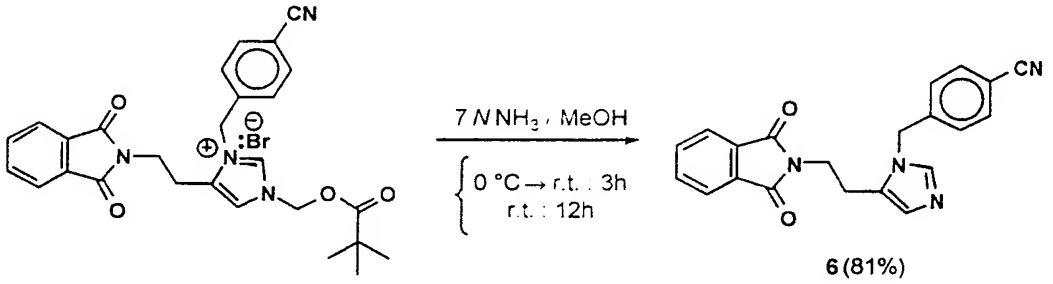


4

12 (94%)

A solution of **4** (3.0 g, 8.4 mmol, 1.0 eq.) and 4-fluorobenzylbromide (2.2 ml, 16.9 mmol, 2.0 eq.) is stirred in anhydrous acetonitrile (50 ml) at 50 °C under a nitrogen atmosphere for 12h. The resulting snow-white suspension is cooled to room temperature and chilled in a refrigerator at -20 °C for one hour. The precipitate is filtered off and thoroughly washed with ice-cold ethyl acetate (4 x 25 ml). The solid is collected and dried under vacuum over P_2O_5 at 50 °C for 12h to give *1-pivaloyloxymethyl-3-(4-fluorobenzyl)-4-(2-phthalimidoethyl)imidazolium bromide* **12** (4.32 g, 7.93 mmol) in 94% yield.

Preparative Example 4.

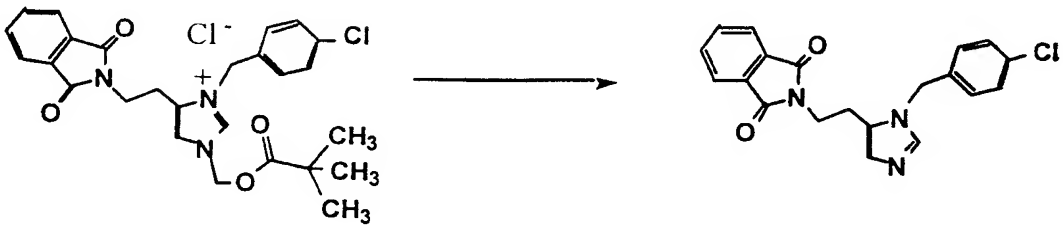


5

6 (81%)

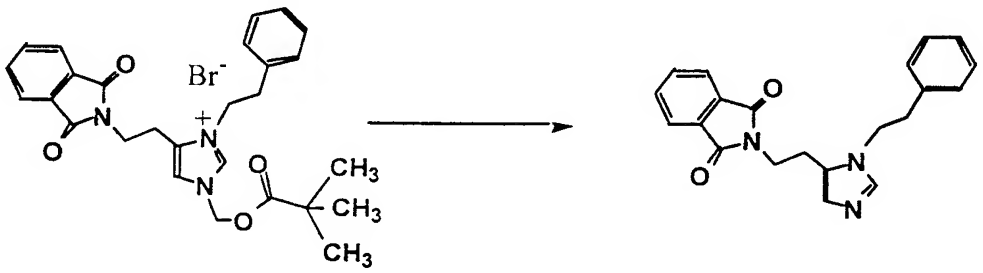
A 7 *N* solution of ammonia in methanol (75 ml, 0.525 mol, 7.25 eq.) is added dropwise over a period of 75 minutes to a stirred solution of **5** (40 g, 0.073 mol, 1.00 eq.) in anhydrous methanol (1000 ml) at 0 °C under a nitrogen atmosphere. The mixture is slowly (3h) warmed to ambient temperature and stirred for another 12h. The volatiles are evaporated under vacuum at 30 °C and the residual white solid is flash-chromatographed (CH_2Cl_2 : 2 *N* NH_3 / MeOH = 90 : 10 v/v) over silica gel to give *N^p-(4-cyanobenzyl)-N^a-phthaloylhistamine* **6** (21 g, 0.059 mol).

Preparative Example 4A. N-[(4-chlorophenyl)methyl]-N-phthaloylhistamine



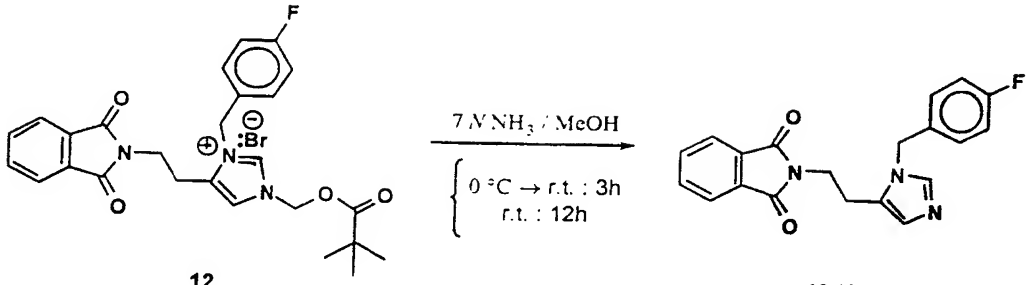
A 7 *N* solution of ammonia in methanol (10 ml, 0.07 mol) is added slowly to a stirred solution of the title compound from Preparative Example 3A (3.2 g, 6.6 mmol) diluted with MeOH (10 mL) at -20°C. The resulting mixture is warmed to room temperature and stirred for another 12 h, then concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 3% MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent to afford the title compound as a sticky solid (1.2 g, 51%, MH^+ = 366).

Preparative Example 4B. N-(4-phenylethyl)-N-phthaloylhistamine



A 7 *N* solution of ammonia in methanol (23 ml, 0.16 mol) is added slowly to a stirred solution of the title compound from Preparative Example 3B (15.8 mmol) diluted with MeOH (60 mL) at -20°C. The resulting mixture is warmed to room temperature and stirred for another 96 h, then concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 3% MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent to afford the title compound (1.6 g, MH^+ = 346).

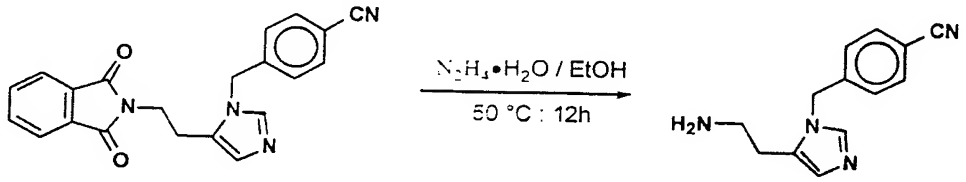
Preparative Example 4C.



12 13 (63%)

A 7 *N* solution of ammonia in methanol (8.0 ml, 55.10 mmol, 7.25 eq.) is added dropwise over a period of 10 minutes to a stirred solution of 12 (4.0 g, 7.35 mmol, 1.00 eq.) in anhydrous methanol (50 ml) at 0 °C under a nitrogen atmosphere. The mixture is slowly (3h) warmed to ambient temperature and stirred for another 12h. The volatiles are evaporated under vacuum at 30 °C and the residual white solid is flash-chromatographed (CH_2Cl_2 : 2 *N* NH_3 / MeOH = 97 : 3 v/v) over silica gel to give *N^p-(4-fluorobenzyl)-N^a-phthaloylhistamine* 13 (1.62 g, 4.63 mmol, 63%) as a snow-white solid.

Preparative Example 5.



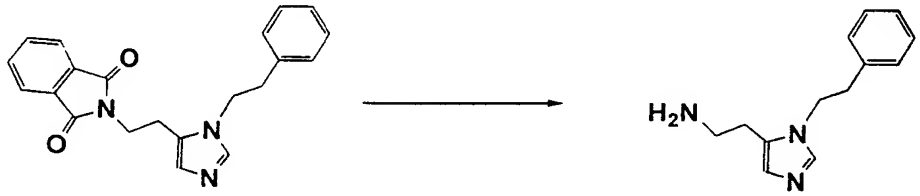
6 7 (85%)

A solution of **6** (21 g, 0.059 mol, 1.0 eq.) and hydrazine monohydrate (15 ml, 0.884 mol, 15.0 eq.) in absolute ethanol (250 ml) is stirred at 50 °C under a nitrogen atmosphere for 12h. The snow-white suspension is cooled to room temperature and chilled in a refrigerator at -20 °C for one hour. The precipitate (phthalyl hydrazide) is filtered off and thoroughly washed with ice-cold ethanol (190 proof, 500 ml). The filtrates are combined and concentrated under vacuum at 30 °C. The residue is subjected to flash column chromatography (CH_2Cl_2 : 2 *N* NH_3 / MeOH = 90 : 10 v/v) over silica gel to give *N^p-(4-cyanobenzyl)histamine* **7** (11.4 g, 0.050 mol, 85%) as a thick, light-brown oil.

Preparative Example 5A. N-[(4-chlorophenyl)methyl]-histamine

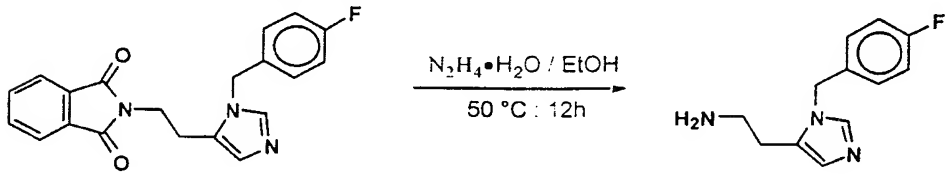
A solution of the title compound from Preparative Example 4A (1.21 g, 3.3 mmol) and hydrazine monohydrate (1.7 ml, 0.033 mol, 10 eq.) in absolute ethanol (20 ml) is stirred at 50 °C under a nitrogen atmosphere for 20 min. The resulting suspension is diluted with ethanol and dichloromethane and filtered. The filtrate is concentrated *in vacuo* to afford the title compound as a yellow oily solid (0.7 g, MH^+ = 236).

Preparative Example 5B. N-(phenylethyl)histamine



A solution of the title compound from Preparative Example 4B (1.54 g, 4.4 mmol) and hydrazine monohydrate (2.2 ml, 0.044 mol, 10 eq.) in absolute ethanol (25 ml) is stirred at 50 °C under a nitrogen atmosphere for 20 min, then at room temperature overnight. The resulting suspension is diluted with ethanol and dichloromethane and filtered. The filtrate is concentrated *in vacuo* to afford the title compound as an oily solid (0.88 g, MH^+ = 216).

Preparative Example 5C.

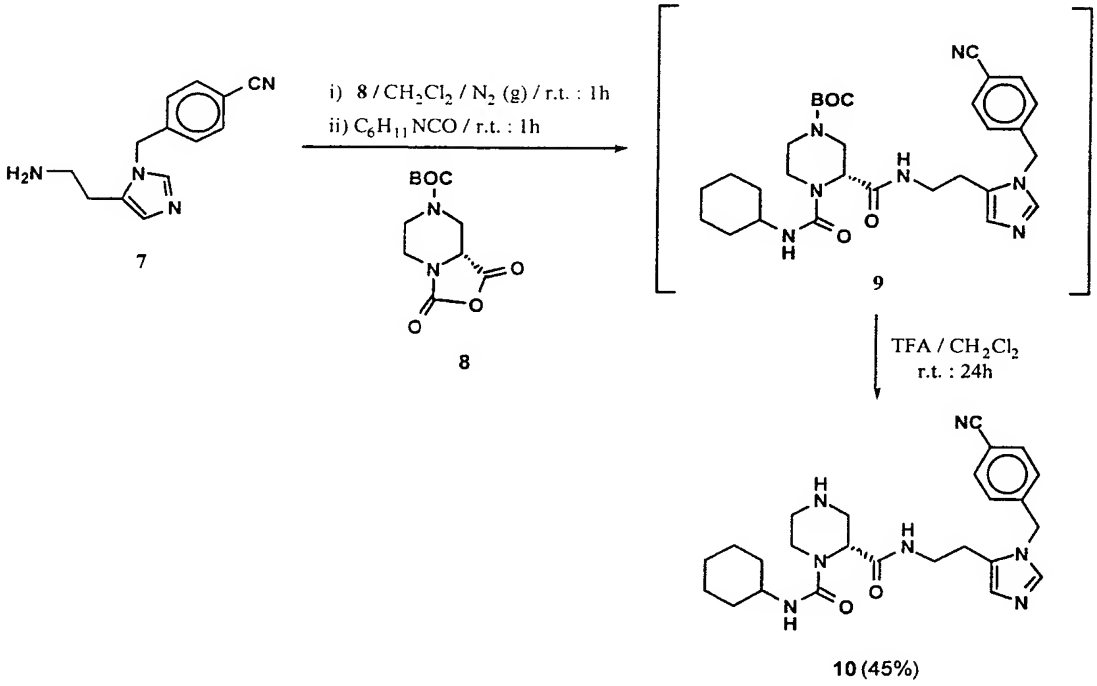


13 14 (87%)

A solution of **13** (1.6 g, 4.6 mmol, 1.0 eq.) and hydrazine monohydrate (1.1 ml, 22.9 mmol, 5.0 eq.) in absolute ethanol (25 ml) was

stirred at 50 °C under a nitrogen atmosphere for 12h. The snow-white suspension was cooled to room temperature and chilled in a refrigerator at -20 °C for one hour. The precipitate (phthalyl hydrazide) was filtered off and thoroughly washed with ice-cold ethanol (190 proof, 50 ml). The filtrates were combined and concentrated under vacuum at 30 °C. The residue was flash column chromatographed (CH_2Cl_2 : 2 *N* NH_3/ MeOH = 90 : 10 v/v) over silica gel to give *N$^{\alpha}$-(4-fluorobenzyl)histamine* **14** (870 mg, 3.97 mmol, 87%) as a brown oil.

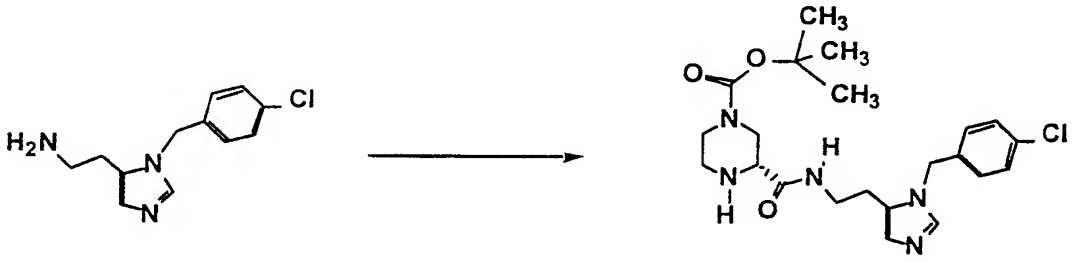
Preparative Examples 8 and 9.



A solution of **7** (1.50 g, 6.63 mmol, 1.0 eq.) in anhydrous dichloromethane (30 ml) is added dropwise over a period of 30 minutes to a stirred solution of anhydride **8** (2.04 g, 7.95 mmol, 1.2 eq.) in anhydrous dichloromethane (30 ml) at room temperature. A stream of nitrogen is bubbled through the solution to expel evolved carbon dioxide. The colorless solution is stirred for one hour amid nitrogen bubbling. Bubbling is terminated and cyclohexyl isocyanate (1.75 ml, 13.26 mmol, 2.0 eq.) is added dropwise over a period of 5 minutes. The brown solution is stirred at room temperature for one hour to give **9** (confirmed by ^{1}H NMR). The

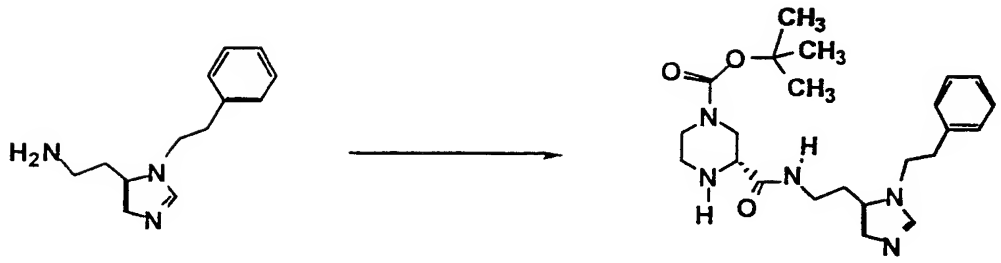
volatiles are removed under vacuum at 30 °C. The residue is taken up in a mixture of trifluoroacetic acid (TFA, 30 ml) and anhydrous dichloromethane (30 ml) and is stirred at ambient temperature under a nitrogen atmosphere for 24h. The mixture is concentrated under vacuum at 30 °C. The residual light-brown oil is taken up in 1 *N* aqueous NaOH solution (100 ml) and extracted with dichloromethane (4 x 25 ml). The combined organic extracts are washed with brine (25 ml), dried over Na_2SO_4, filtered, and concentrated under vacuum at 30 °C. The resulting oil is flash-chromatographed (CH_2Cl_2 : 2 *N* NH_3/ MeOH = 90 : 10 v/v) over silica gel to give *N2-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-N1-cyclohexyl-1,2(R)-piperazinedicarboxamide* **10** (1.34 g, 2.95 mmol) as a light-yellow foam.

Preparative Example 10A. N4-(1,1-dimethylethyloxycarbonyl)-N2-[2-[1-[(4-chlorophenyl)methyl]-1H-imidazol-5-yl]ethyl]-1,2(R)-piperazinecarboxamide



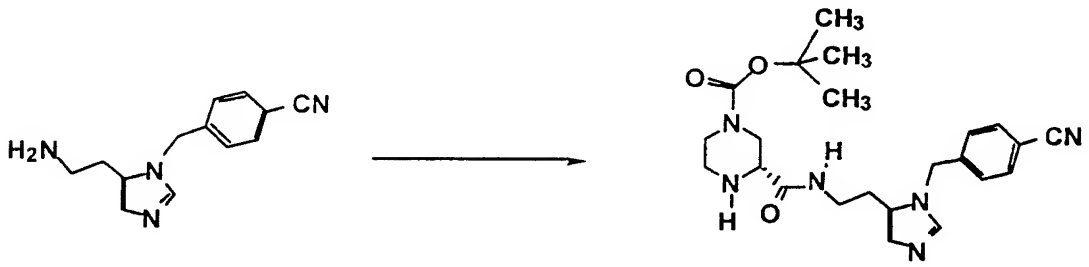
A solution of the title compound from Preparative Example 5A (0.695 g, 2.94 mmol) and the anhydride from Preparative Example (0.75 g, 2.94 mmol) dissolved in anhydrous dichloromethane (10 ml) is stirred at room temperature overnight. Additional anhydride (0.1 g) is added and after 1 hr the reaction mixture is diluted with CH_2Cl_2 and extracted with 1*M* HCl (aq). The aqueous phase is basified with 1*N* NaOH (aq), extracted with CH_2Cl_2 and the organic phase dried over anhydrous $MgSO_4$. After filtration, the organic phase is concentrated *in vacuo* to afford a white foam (0.744 g, MH^+ = 448).

Preparative Example 10B. N4-(1,1-dimethylethyloxycarbonyl)-N2-[2-[1-(phenylethyl)-1H-imidazol-5-yl]ethyl]-1,2(R)-piperazinecarboxamide



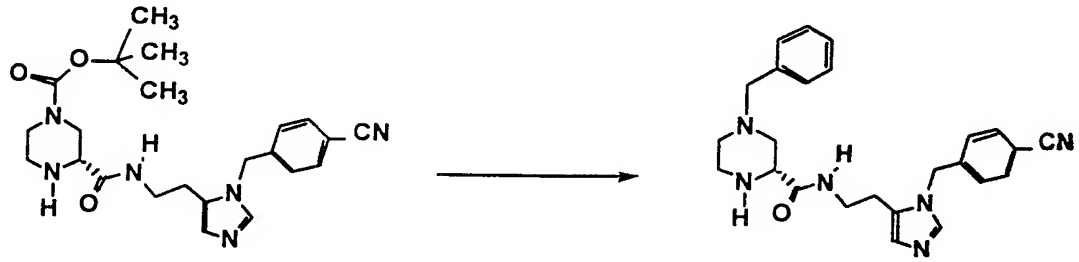
A solution of the title compound from Preparative Example 5B (0.874 g, 4.04 mmol) and the anhydride from Preparative Example (1.04 g, 4.04 mmol) dissolved in anhydrous dichloromethane (10 ml) is stirred at room temperature overnight. Additional anhydride (0.23 g) is added and after 1 hr the reaction mixture is diluted with CH_2Cl_2 and extracted with 1*M* HCl (aq). The aqueous phase is basified with 1*N* NaOH (aq), extracted with CH_2Cl_2 and the organic phase dried over anhydrous $MgSO_4$. After filtration, the organic phase is concentrated *in vacuo* to afford a white foam (1.22 g, 71%, MH^+ = 428).

Preparative Example 10. N4-(1,1-dimethylethyloxycarbonyl)-N2-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-1,2(R)-piperazinecarboxamide



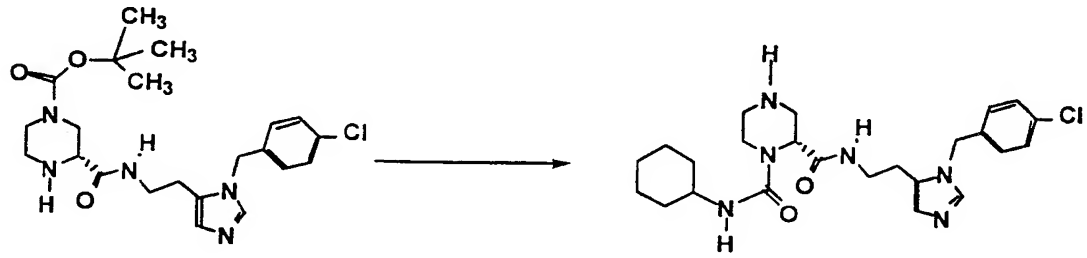
A solution of the title compound from Preparative Example 5 (7.8 g, 34.5 mmol), triethylamine (10 mL) and the anhydride from Preparative Example (10 g, 39.0 mmol) dissolved in anhydrous dichloromethane (300 ml) is stirred at room temperature overnight. The reaction mixture is concentrated *in vacuo*, diluted with CH_2Cl_2 and extracted with 1*M* HCl (aq). The aqueous phase is basified with 1*N* NaOH (aq), extracted with CH_2Cl_2 and the organic phase dried over anhydrous $MgSO_4$. After filtration, the organic phase is concentrated *in vacuo* to afford the title compound (10.0 g, MH^+ = 448).

Preparative Example 11. N2-[2-[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]ethyl]-N4-phenyl-1,2(R)-piperazinecarboxamide



A solution of the title compound from Preparative Example 10 (5 g, 1.1.4 mmol) dissolved in anhydrous dichloromethane (50 ml) and trifluoroacetic acid (10 ml) is stirred at room temperature for 1 hr, then concentrated *in vacuo*. The residue is combined with benzaldehyde (1.4 mmol) and diluted with glacial acetic acid (25 mL) and anhydrous dichloromethane (100 ml), then cooled to 0°C. Sodium triacetoxyborohydride (4.83 g, 22.8 mmol) is added and the resulting mixture is stirred at 0°C for 2 h, then at room temperature overnight. The reaction mixture is concentrated *in vacuo*, diluted with dichloromethane and extracted with 1*N* HCl (aq). The aqueous phase is basified with 1*N* NaOH (aq) and extracted with dichloromethane, then dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*. Flash column chromatography (silica gel) using 10% MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent affords the title compound (1.5 g, MH^+ = 428).

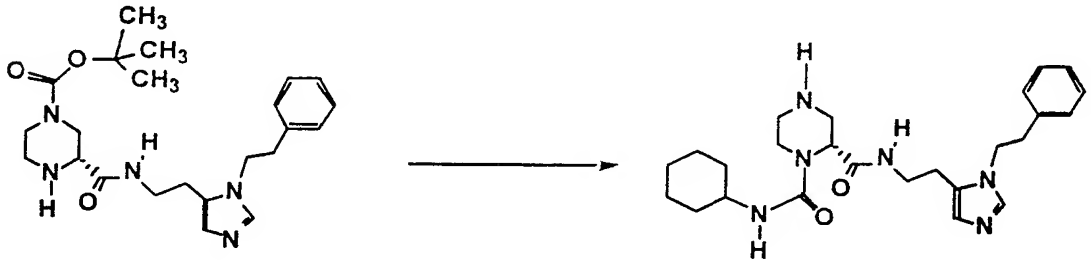
Preparative Example 12. N2-[2-[1-[(4-chlorophenyl)methyl]-1H-imidazol-5-yl]ethyl]-N1-cyclohexyl-1,2(R)-piperazinecarboxamide



To a solution of the title compound from Preparative Example 10A (0.30 g, 0.67 mmol) dissolved in anhydrous dichloromethane (3 ml) is added cyclohexylisocyanate (0.09 mL, 0.7 mmol) and the resulting solution

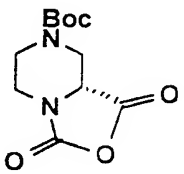
was stirred at room temperature for 30 min, then concentrated *in vacuo*. The resulting residue is diluted with dichloromethane (3 ml) trifluoroacetic acid (3 ml). The solution is stirred at room temperature overnight, then concentrated *in vacuo*, diluted with dichloromethane and washed with 1*N* NaOH (aq). The organic phase is dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow foam (0.319 g, MH^+ = 473).

Preparative Example 12A. N2-[2-[1-(phenylethyl)-1H-imidazol-5-YL]ethyl]-N1-cyclohexyl-1,2(R)-piperazinedicarboxamide

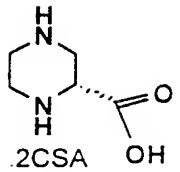


To a solution of the title compound from Preparative Example 10B (0.33 g, 0.77 mmol) dissolved in anhydrous dichloromethane (3 ml) is added cyclohexylisocyanate (0.11 mL, 0.9 mmol) and the resulting solution is stirred at room temperature for 30 min, then concentrated *in vacuo*. The resulting residue is diluted with dichloromethane (3 ml) trifluoroacetic acid (3 ml). The solution is stirred at room temperature overnight, then concentrated *in vacuo*, diluted with dichloromethane and washed with 1*N* NaOH (aq). The organic phase is dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow foam (0.338 g, MH^+ = 453).

Preparative Example 13.

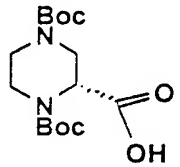


Step a. 2-R-carboxyl-piperazine-di-(R)-(-)-camphorsulfonic



To 2.5 kg of (R)-(-)-camphorsulfonic acid stirring at 60°C in 1250 ml of distilled water are added a soution of the potassium salt of 2-carboxyl-piperazine (565 gm, 3.35 mol). The mixture is allowed to stir at 95 °C until completely dissolved. The solution is allowed to stand at ambient temperature for 48 hrs. The resulting precipitate is filtered to obtain 1444 gm of damp solid. The solids are then dissolved in 1200 ml of distilled water and heated on a steam bath until all solids dissolved. The hot solution is then set aside to cool slowly for 72 hrs. The crystalline solids are filtered to give 362 gm of pure product as a white crystalline solid. $[a]_D$=-14.9 °

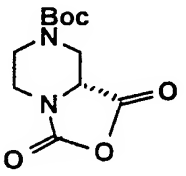
Step b. N,N-di-tert.butoxycarbonyl-2-R-carboxyl-piperazine



2-R-carboxyl-piperazine-di-(R)-(-)-camphorsulfonic (362 gm, 0.608 mol) from Step a. is dissolved in 1.4 L of distilled water and 1.4 L of methanol. 75 ml of 50% NaOH are dripped in to the stirred reaction mixture to obtain an about pH= 9.5 solution. To this solution is added di-tert.butyl-dicarbonate (336 gm, 1.54 mol) as a solid. The pH drops to about 7.0. The pH of the reaction mixture is maintained at 9.5 with 50% NaOH (total of 175 ml), and the reaction mixture is stirred for 2.5 hours to obtain a white precipitate. The reaction mixture is diluted to 9 L with ice/water followed by washing with 2 L of ether. The ether is discarded and the pH of the aqueous layer isadjusted to pH 3.0 by the portionwise addition of solid citric acid. The acidified aqueous layer is then extracted with dichloromethane 3X with 2L. The organic layers are combined, dried

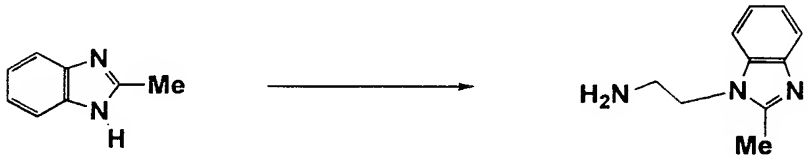
over sodium sulfate, filtered and evaporated to obtain 201.6 gm of title compound as a white glassy solid. FABMS (M+1)=331

Step c. "N-Boc-piperazine-2-amidoanhydride"



To an ice cold solution N,N-dimethylformamide (49.6 ml) is added, dropwise, thionylchloride (46.7 ml) over a period of 5 minutes in a 5 L round bottom flask under a nitrogen atmosphere The reaction mixture is allowed to stir for 5 min. and the ice bath removed and the reaction mixture allowed to stir at ambient temperature for 30 min. The reaction mixture is cooled again in an ice bath and a solution of of N,N-di-butoxycarbonyl-2-R-carboxyl-piperazine (201.6 gm, 0.61 mmol) from Step b. in 51.7 ml of pyridine and 1.9 L of acetonitrile are cannulated into the reaction mixture. The reaction mixture is allowed to warm to ambient to obtain a yellowish turbid solution. After stirring at ambient temperature for 18 hours, the reaction mixture is filtered and the filtrate poured into ice water (7L) and then extracted with 4X 2 L of ethylacetate, dried over sodium sulfate, filtered and evaporated to dryness under vacuo to obtain 115.6 gm of the title product as a white solid. FABMS (M+1)=257.

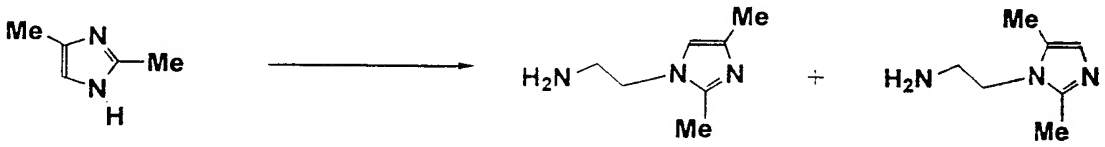
Preparative Example 14. [2-(2-methyl-1H-benzimidazol-1-yl)ethyl]amine



A mixture of 2-methylbenzimidazole (4.93 g, 37.3 mmol), 2-chloroethylamine hydrochloride (4.67 g, 40.3 mmol), tetrabutylammonium sulfate (0.51 g, 1.5 mmol), sodium hydroxide (5.37 g, 134.2 mmol) and acetonitrile (80 mL) are stirred at reflux for 48 hrs. The resulting mixture is cooled to room temperature, filtered and concentrated *in vacuo*. The residue is purified by flash column chromatography (silica gel) using 1-3%

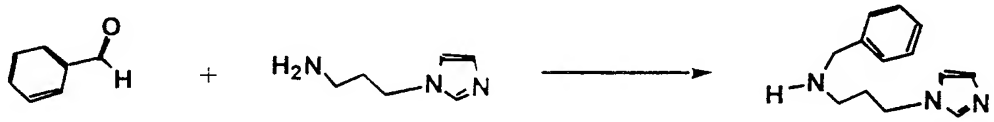
MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent to afford the title compound (3.56 g, MH^+ = 176).

Preparative Example 15. [2-(2,4-dimethylimidazol-1-yl)ethyl]amine and [2-(2,5-dimethylimidazol-1-yl)ethyl]amine



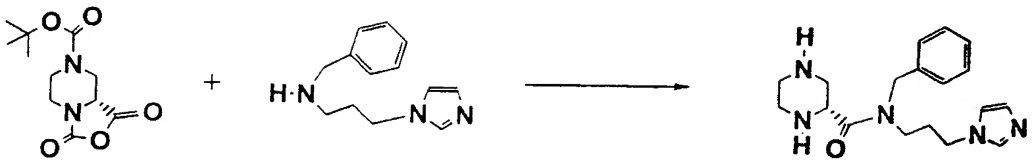
Following a similar procedure used in Preparative Example 14, but using 2,4-dimethylimidazole instead of 2-methylbenzimidazole, the title compounds were prepared as a mixture of regioisomers (10.7 g, MH^+ =).

Preparative Example 16. 3-(1H-imidazol-1-yl)propyl-phenylmethylamine



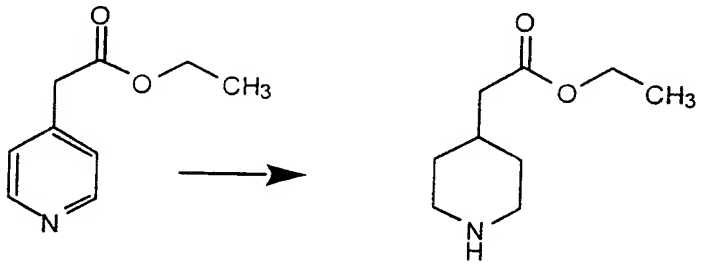
A mixture of 1-(3-aminopropyl)imidazole (Aldrich, 37.1 g, 297 mmol), benzaldehyde (30 g, 283 mmol), 3Å molecular sieves (50 g), sodium acetate (24.1 g, 283 mmol) and anhydrous methanol (700 mL) are stirred at room temperature under N_2 overnight. The mixture is cooled to 0°C and sodium borohydride (10.9 g, 288 mmol) is added portionwise over 1 hour. The mixture is stirred at room temperature for 3 hours. The mixture is filtered through celite, washed with methanol, and concentrated *in vacuo* to give a residue which is diluted with dichloromethane and washed with 10% aqueous sodium hydroxide. The organic phases are washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give the title compound as a pale yellow oil (56.3 g, MH^+ = 216).

Preparative Example 17. 2(R)-[[[3-(1H-imidazol-1-yl)propyl](phenylmethyl)amino]carbonyl]piperazine



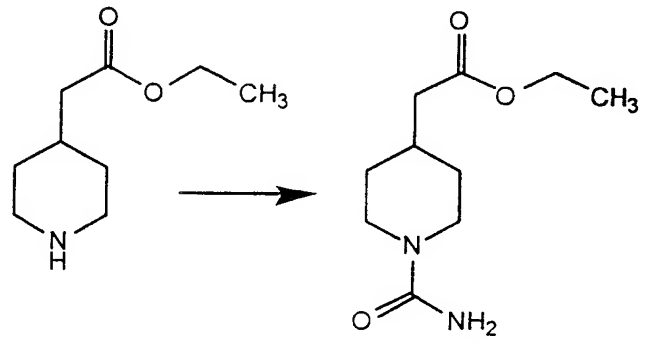
A mixture of the title compound from Preparative Example 16 (1.34 g, 6.2 mmol), the title compound from Preparative Example 13 (1.6 g, 6.2 mmol), triethyl amine (1.3 mL, 9.3 mmol) and anhydrous CH_2Cl_2 (10 mL) are stirred at room temperature for 48 hrs. Trifluoroacetic acid (10 mL) is added and the resulting mixture is stirred for an additional 1.5 hrs. Aqueous NaOH (1N) is added dropwise to neutralize the reaction mixture and the resulting mixture is extracted with CH_2Cl_2. The organic phase is dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a residue which is purified by flash column chromatography (silica gel) using 1% MeOH-99% CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (520 mg, MH^+ = 328).

Preparative Example 18. Ethyl 4-piperidinyl acetate



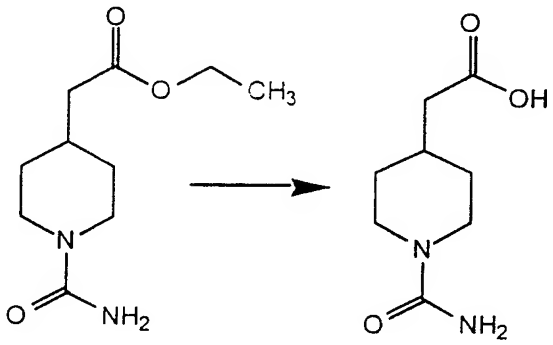
Ethyl 4-pyridyl acetate (4.5g, 27.24mmoles) is placed in a 500mL Parr bottle and dissolved in anhydrous EtOH (70mL). To the bottle is added 10% Palladium on charcoal (1.0 g). The bottle is put on a hydrogenator and the contents shaken under 55 psi hydrogen pressure at 25°C for 94h. The mixture is filtered through Celite® and washed with 4x40mL anhydrous EtOH. The filtrate is rotovapped down and the residue chromatographed on silica gel using 3% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give 2.944g of the title compound.

Preparative Example 19. Ethyl 1-aminocarbonyl-4-piperidinyl acetate



Ethyl 4-piperidinyl acetate (500mg; 2.92mmoles) is dissolved in anhydrous CH_2Cl_2 (25mL). To the stirring solution is added trimethylsilyl isocyanate (5.9mL; 43.8mmoles) and the solution is stirred at 25°C for 17h. The solution is worked up in CH_2Cl_2-saturated $NaHCO_3$ and the product chromatographed on silica gel using 2→3%(conc. NH_4OH in methanol)dichloromethane as the eluant to give 622mg of the title compound.

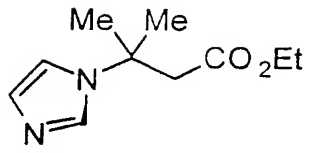
Preparative Example 20. 1-Aminocarbonyl-4-piperidinylacetic acid



Ethyl 1-aminocarbonyl-4-piperidinyl acetate (153.6mg, 0.717mmoles) is dissolved in anhydrous CH_2Cl_2 (3.58mL) and EtOH (3.58mL). To the solution is added 1.0M LiOH (1.73mL, 1.73mmoles) and the mixture is stirred at 50°C for 5.5h. The mixture is cooled quickly to 25°C and 1.0N HCl (2.02mL, 2.02mmoles) is added and the mixture stirred for 5 minutes and then rotovapped to dryness to give the title compound which is used without further purification.

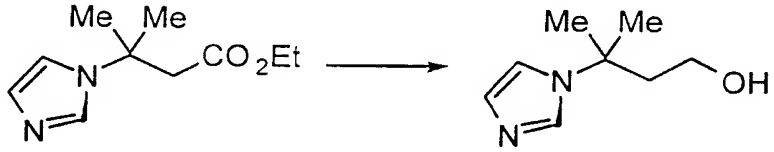
Preparative Example 21.

Step A:



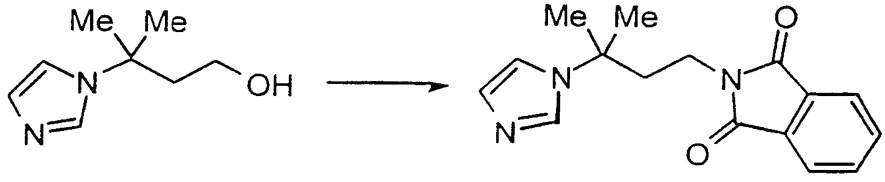
Ethyl 2,2-dimethyl acrylate (50.0g, 2.0 eq.) is stirred with imidazole (13.28g, 200 mmol) at 90° for 48 hours. The resulting solution is cooled, diluted with water (150 mL) and CH_2Cl_2 (150 mL) and separated. The aqueous layer is washed with CH_2Cl_2 (2 x 75 mL) and the combined organics are dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture is purified by flash chromatography using a 10% MeOH in CH_2Cl_2 solution as eluent to give pure product as a clear oil (11.27g).

Step B:



A solution of the title compound from Step A (10.0g, 50.96 mmol) is treated with $LiAlH_4$ (51 mL, 1M solution in ether, 1.0 eq.). The reaction mixture is stirred one hour at room temperature before quenching by the dropwise addition of saturated Na_2SO_4 (~3.0 mL). The resulting slurry is dried with Na_2SO_4 (solid), diluted with EtOAc (100 mL) and filtered through a plug of Celite. The filtrate is concentrated to give a yellow oil (6.87, 87% yield) which is used without further purification.

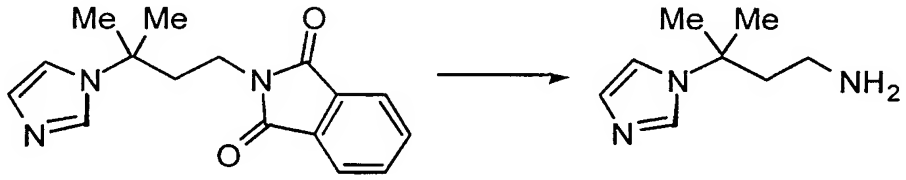
Step C:



To a solution of the title compound Step B (6.85g, 44.42 mmol), phthalimide (7.19g, 1.1 eq.), and triphenylphosphorous (Ph_3P) (12.82g, 1.1 eq.) in THF (200 mL) at 0° C is added DEAD(7.69 mL, 1.1 eq.) over 10

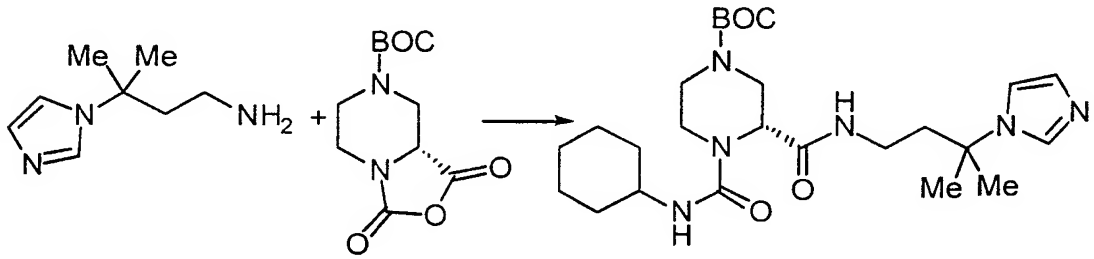
minutes. The resulting solution is warmed to room temperature and stirred 48 hours. The reaction mixture is concentrated under reduced pressure and the product isolated by crystallization from CH_2Cl_2/Et_2O to give a white solid (10.03 g).

Step D:



A solution of the title compound from Step C (9.50g, 33.53 mmol) and (N_2H_4) (1.25 mL, 1.2 eq.) in EtOH (100 mL) is heated at reflux 4 hours. The resulting slurry is cooled, filtered, and the filtrate concentrated under reduced pressure. The crude product is purified by flash chromatography using a 15% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to give a pale yellow oil (2.80g).

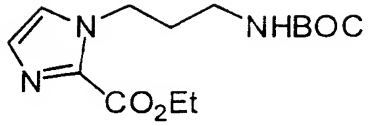
Preparative Example 22.



Piperazine anhydride (0.28g, 1.0 eq.) is added portionwise to a solution of the title compound from Step D of Preparative Example 21 (0.17g, 1.2 mmol) in CH_2Cl_2 (5.0 mL) and the resulting solution is stirred 10 minutes at room temperature before adding cyclohexyl isocyanate (0.21 mL, 1.5 eq.). After stirring at room temperature 15 minutes, the reaction mixture is quenched by the addition of MeOH (1 mL), concentrated *in vacuo*, and purified by flash chromatography using a 10% MeOH in CH_2Cl_2 solution as eluent to yield a white solid (0.46g). mp= 71-74 °C.

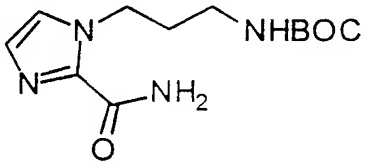
Preparative Example 23.

Step A:



n-BuLi (2.79 mL; 1.75M in hexanes; 2.2 eq.) is added dropwise to a solution of N-BOC aminopropylimidazole (0.50 g, 2.22 mmol) in THF (15 mL) at -78 °C. The resulting solution is warmed to -20 °C and stirred two hours before adding TMSCl (0.65 mL, 2.3 eq.). The reaction mixture is warmed to room temperature, stirred one hour, recooled to -78 °C and treated with $ClCO_2Et$ (0.25g, 1.2 eq.). The resulting solution is warmed to room temperature and stirred 60 hours. The reaction is quenched by the addition of water (10 mL) and extracted with CH_2Cl_2 (3 X 20 mL). The combined organics are dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product is purified by flash chromatography using a 5% MeOH in CH_2Cl_2 solution as eluent (0.35g, 53% yield).

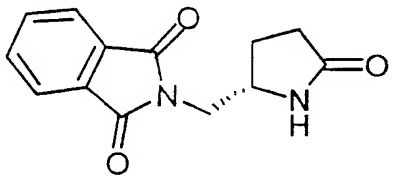
Step B:



A solution of the title compound from Step A (0.35g, 1.18 mmol) is stirred in EtOH (10 mL) and 30% NH_4OH (2 mL) for 24 hours. The reaction mixture is concentrated under reduced pressure and purified by flash chromatography using neat EtOAc as eluent (0.23g).

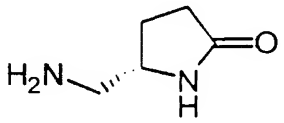
Preparative Example 24.

Step A:



By using essentially the same procedure set forth in Step C of Preparative Example 21 except using S-(+)-5-hydroxymethyl-2-pyrrolidinone (1.0g, 8.69 mmol) in place of the title compound is prepared (1.50g).

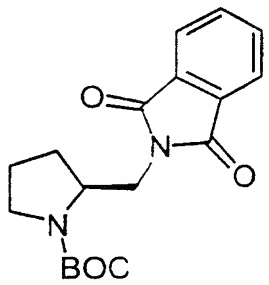
Step B:



By using essentially the same procedure as set forth in Step D of Preparative Example 21 except using the title compound from Step A of Preparative Example 24 (1.50g, 6.14 mmol), the title compound is prepared (0.59 g).

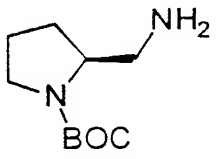
Preparative Example 25.

Step A:



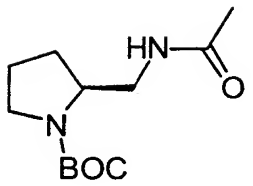
By essentially the same procedure set forth in Step C of Preparative Example 21 except using N-BOC-S-prolinol (0.50g, 2.48 mmol), the title compound is prepared (0.59 g).

Step B:



By essentially the same procedure set forth in Step D of Preparative Example 21 except using the title compound from Step A of Preparative Example 25 (0.59 g, 1.79 mmol), the title compound is prepared (0.36g).

Step C:



Ac_2O (0.20 mL, 1.2 eq.) is added to the title compound from Step B Preparative Example 25 (0.36 g, 1.80 mmol) and TEA (0.30 mL, 1.2 eq.) in CH_2Cl_2 (8.0 mL). The resulting solution is stirred 2 hours and quenched by the addition of saturated $NaHCO_3$ (10 mL). The resulting solution is extracted with CH_2Cl_2 (2 X 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product is purified by flash chromatography eluting first with neat EtOAc followed by 5% MeOH in EtOAc (0.23g).

ASSAYS

1. In vitro enzyme assays: FPT IC_{50} (inhibition of farnesyl protein transferase, in vitro enzyme assay) are determined by the methods disclosed in WO/10515 or WO 95/10516. The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent (IC_{50} <10 μM) inhibitors of Ras-CVLS farnesylation by partially purified rat brain FPT.

Compounds of Examples 1-3, 5-28, 28A-28X, 28Y1, 28Y2, 28Z, 28Z1, 28Z2, 29-57, 57A, 58-62, and 64-67 had an FPT IC_{50} within the range of 0.18nM to 4000nM (nM represents nanomolar).

Compounds of Examples 1, 5, 6, 8-17, 20-28, 28C, 28E, 28F, 28G, 28I, 28M, 28O, 28P, 28Q, 28R, 28S, 28T, 28V, 28Y1, 28Y2, 29, 31, 32, 34, 36-38, 42, 43, 47, 53-56, 58, 61 and 64 had an FPT IC_{50} within the range of 0.18nM to 21nM.

Compounds 20, 25, 26, 27, 28, 28O, 54 and 55 had an FPT IC_{50} within the range of 0.18nM to 1.5nM.

Additional assays can be carried out by following essentially the same procedure as described above, but with substitution of alternative indicator tumor cell lines in place of the T24-BAG cells. The assays can be conducted using either DLD-1-BAG human colon carcinoma cells expressing an activated K-ras gene or SW620-BAG human colon carcinoma cells expressing an activated K-ras gene. Using other tumor cell lines known in the art, the activity of the compounds of this invention against other types of cancer cells could be demonstrated.

Soft Agar Assay:

Anchorage-independent growth is a characteristic of tumorigenic cell lines. Human tumor cells can be suspended in growth medium containing 0.3% agarose and an indicated concentration of a farnesyl transferase inhibitor. The solution can be overlayed onto growth medium solidified with 0.6% agarose containing the same concentration of farnesyl transferase inhibitor as the top layer. After the top layer is solidified, plates can be incubated for 10-16 days at 37°C under 5% CO_2 to allow colony outgrowth. After incubation, the colonies can be stained by overlaying the agar with a solution of MTT (3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide, Thiazolyl blue) (1 mg/mL in PBS). Colonies can be counted and the IC_{50}'s can be determined.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg and most preferably from about 0.01 mg to about 250 mg, according to the particular application.

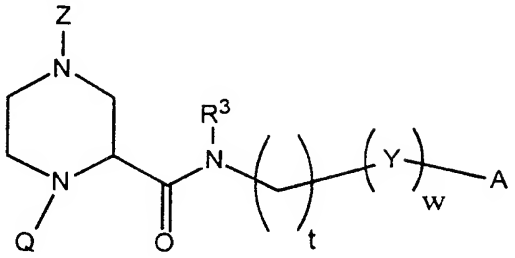
The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.04 mg/day to about 4000 mg/day, in two to four divided doses.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

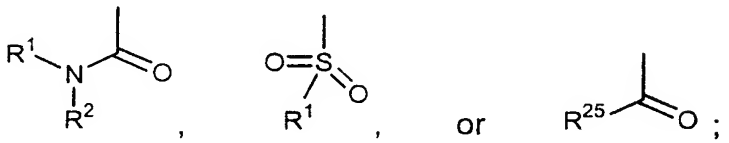
1. A compound of the formula:



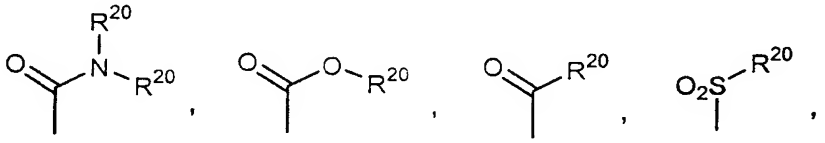
(1.0)

or a pharmaceutically acceptable salt or solvate thereof,

wherein Q is:



Z represents hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl,



heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, or $-CY^3Y^4$ wherein Y^3 and Y^4 independently represent alkyl and aryl or Y^3 and Y^4, together with the attached carbon atom (-C), can form a cycloalkyl or a cycloalkenyl ring;

wherein R^1, R^2, R^3, R^{20}, R^{22}, R^{30} and R^{32} independently represent hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R^{25} can represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl or -OR^{40} wherein R^{40} can represent alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

Y represents aryl, heteroaryl, heterocycloalkyl or cycloalkyl,

t is zero, 1, 2 or 3;

w is zero or 1; and

A is nothing, hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, cyano, heteroaryl or heteroarylalkyl.

2. The compound of Claim 1 selected from any of the title compounds of Examples 1-237.

3. The compound of Claim 1 selected from the title compounds of Examples 1, 3, 4, 5, 6, 9, 10, 11, 13, 14 and 15.

4. A pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound of any of Claims 1 to 3 in combination with a pharmaceutically acceptable carrier.

5. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of any of Claims 1 to 3.

6. The method of Claim 5 wherein the the cells inhibited are tumor cells.

7. The method of Claim 5 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells,

thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or prostate tumor cells, melanoma tumor cells, breast tumor cells or colon tumors cells.

8. The method of Claim 5 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of ras farnesyl protein transferase.

9. The method of Claim 5 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

10. The use of a compound of any of Claims 1 to 3 for the manufacture of a medicament for inhibiting the abnormal growth of cells.

11. The use of Claim 10 wherein the the cells inhibited are tumor cells.

12. The use of Claim 10 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or prostate tumor cells, melanoma tumor cells, breast tumor cells or colon tumors cells.

13. The use of Claim 10 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of ras farnesyl protein transferase.

14. The use of Claim 10 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

15. The use of a compound of any of Claims 1 to 3 for the inhibition of pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells,

epidermal carcinoma tumor cells, bladder carcinoma tumor cells or prostate tumor cells, melanoma tumor cells, breast tumor cells or colon tumors cells.

16. The use of a compound of any of Claims 1 to 3 for the inhibition of ras farnesyl protein transferase.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/27958

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/12 C07D401/14 C07D241/04 A61K31/496 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 13646 A (MERCK) 23 June 1994 (1994-06-23) page 1 -page 46; claims; examples 3,4,6	1,4
X	J.G. BREITENBUCHER: "GENERATION OF A PIPERAZINE-2-CARBOXAMIDE LIBRARY:" TETRAHEDRON LETTERS., vol. 39, no. 11, 1998, pages 1295-8, XP004107918 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4039 page 1295 -page 1297	1
A	WO 95 00497 A (MERCK) 5 January 1995 (1995-01-05) cited in the application page 142; claims; example 15	1,4-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2000	27/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/27958

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 5 880 128 A (R.J. DOLL) 9 March 1999 (1999-03-09) column 60 -column 85	1,2,4-16

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/US 99/27958

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9413646 A	23-06-1994	US 5344830 A	06-09-1994
		AU 5603094 A	04-07-1994
WO 9500497 A	05-01-1995	AU 675145 B	23-01-1997
		AU 7041294 A	17-01-1995
		CA 2165176 A	05-01-1995
		EP 0703905 A	03-04-1996
		JP 9500109 T	07-01-1997
		US 5736539 A	07-04-1998
		ZA 9404326 A	14-12-1995
US 5880128 A	09-03-1999	NONE	